106-02-24

3-D Pancreatic History in Health and Disease

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Abstract

Pancreas features extensive ductal and neurovascular networks in association with acini and islets to perform exocrine and endocrine functions. However, due to the dispersed nature of the network architecture, standard microtome-based histology cannot provide a globe view of the pancreatic tissue networks in health and disease. In this talk, we will discuss our approach of using 3-D histology to examine the mouse and human pancreatic microstructure, vasculature, and innervation. Examples will be given on characterization of mouse models of diabetes and pre-cancerous/cancerous lesions and how to reveal neurovascular tissues and fatty infiltration in human pancreas. The long-term goal of our work is to establish “3-D histology” as a preferred method for tissue analysis to characterize the unknown details of pancreatic microenvironment in metabolic disorders and duct lesion progression.

106-03-03

Factors Regulating Inflammation and B cell Responses

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Abstract

The etiology contributing to skin inflammatory disorders is poorly understood. We showed that transcriptional repressor B lymphocyte–induced maturation protein-1 (Blimp-1) plays a novel role in restraining steady-state epidermal immune reactions by decreasing the expression of cytokine/chemokine, including G-CSF, in epidermal keratinocytes through directly repressing two AP-1 family members, Fos and Fosl1, in basal conditions. Furthermore, the expression of Blimp-1 was reduced in the skin lesions of some cases of human eczema, suggesting that preventing the reduction in Blimp-1 may be a therapeutic direction for certain types of cutaneous inflammation.

In fact, Blimp-1 was first demonstrated for its essential role in the generation of antibody-producing plasma cells. Blimp-1 orchestrates plasma cell differentiation by silencing the gene expression program of mature B cells. We showed the molecular mechanism underlying Blimp-1 suppression of mature B-cell gene expression and how the post-transcriptional and post-translational modification (PTM) of Blimp-1 may participate in this regulatory effect. In addition to controlling the generation of plasma cells, long-lived plasma cells in the bone marrow require the continuous presence of Blimp-1. Further studies have uncovered the molecular mechanisms by which Blimp1 suppresses downstream effector targets in maintaining plasma cell survival. These findings revealed the complex regulatory mechanisms by which Blimp-1 possesses to shape humoral immunity and maintain the survival of plasma cells.

In a separate line, we study the effects of PTM on B cell activation. O-linked β-Nacetylglucosamine (O-GlcNAc) modification (O-GlcNAcylation) adds a GlcNAc to serine or threonine residue of nuclear and cytosolic proteins. O-GlcNAcylation is catalyzed by O-linked N-acetylglucosamine transferase (OGT) and can be reversely removed by O-GlcNAcase (OGA). O-GlcNAcylation has influence on other PTMs, in particular protein phosphorylation, thus adding another layer of complexity to the networks of PTMs that regulate the important cellular functions. We find that OGlcNAcase inhibition enhances B cell activation and apoptosis induced by B cell receptor (BCR) cross-linking. The functional interplay between protein OGlcNAcylation and phosphorylation in activated primary B cells was also deciphered by our proteome-scale study. Specifically, we found that O-GlcNAcylation at S209 of lymphocyte specific protein-1 (Lsp1) is required for the recruitment of its kinase PKCβ1 to induce S243 phosphorylation, the temporal regulation of which is crucial for inducing apoptosis in activated B cells. Therefore, O-GlcNAcylation of Lsp1 transmits critical signals for initiating apoptosis after BCR ligation.

106-03-10

Parkinson's Disease: Electrophysiological Perspectives & the Molecular Bases

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Abstract

Parkinson's disease (PD) is the most prevalent hypokinetic movement disorder, and symptomatic PD pathogenesis has been ascribed to imbalances between the direct and indirect pathways in the basal ganglia circuitry. We found that inhibition of NMDAergic cortico-subthalamic transmission ameliorates parkinsonian motor deficits without eliciting any vivid turning behavior and abolishes electrophysiological abnormalities, including excessive subthalamic bursts, cortico-subthalamic synchronization, and in situ beta synchronization in both the motor cortex and subthalamus (STN). Premotor cortex stimulation revealed that cortico-subthalamic transmission is deranged in PD and directly responsible for the excessive stimulation-dependent bursts and time-locked spikes in the STN, explaining the genesis of PD-associated pathological bursts and synchronization, respectively. Moreover, application of a dopaminergic agent via a microinfusion cannula localized the therapeutic effect to the STN, without correcting striatal dopamine deficiency. These data suggest that deranged cortico-subthalamic transmission via the NMDA receptor plays a central role in the pathophysiology of parkinsonian motor deficits. In this regard, we further showed that STN burst-firing and beta oscillations/ synchronization are two independent mechanisms regulated by different NMDA receptors in STN, namely GluN2B and GluN2A, respectively. The major pathophysiological basis underlying parkinsonian bradykinesia therefore is more likely a feed-forward event coded by neuronal firing patterns rather than interactive neural oscillations. This novel insight into bradykinesia may not only advance the fundamental concepts of motor control but also contribute to more effective and selective therapeutic maneuvers for PD.

Reference:

1. Pan, M.-K., Tai, C.-H., Lin, W.-C., Pei, J.-C., Lai, W.-S., and Kuo, C.-C. (2014) Deranged NMDAergic cortico-subthalamic transmission underlies parkinsonian motor deficits. *Journal of Clinical Investigation* 124(10):4629-4641

2. Pan, M.-K., Kuo, S.-H., Tai, C.-H., Liou, J.-Y., Pei, J.-C., Chang, C.-Y., Wang, Y.-M., Liu, W.-C., Wang, T.-R., Lai, W.-S., and Kuo, C.-C. (2016) Neuronal firing patterns outweigh circuitry oscillations in parkinsonian motor control. Journal of Clinical Investigation 126(12):4516-4526

106-03-17

Cellular and Metabolic Signaling in Human Cancers

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Abstract

The proliferation and survival of both normal and cancer cells require continuous protein synthesis, which in turn depend on adequate supply of 20 amino acids (AAs). The fact that the rapid tumor expansion co-opts with an increased metabolic demand has led to the development of AA-restriction-based therapeutic strategies. If we temporarily restrict specific AAs and keep high levels of others, the specific deficiency triggers autophagy-dependent and -independent proteolysis to force cells to obtain adequate levels of any and each of the 20 AAs. However, an effective nutrient-restriction cancer therapy has not been fully exploited and it lacks studies addressing the underlying mechanism for developing such a selective amino acid restrictive therapy. Although all cancers have undergone extensive genetic, epigenetic and post-translational alterations, accumulating evidence has portrayed a common phenomenon of *intrinsic arginine restriction* that multiple tumor cells become auxotrophic for arginine and become sensitive to arginine restriction as endogenous arginine, synthesized from citrulline with aspartate by argininosuccinate synthetase1 (ASS1) and argininosuccinate lyase (ASL), is not sufficient to support the increased demand in highly proliferating tumor cells. Based on this feature, we propose to develop dietary arginine restriction as a non-pharmacological *extrinsic arginine restriction* strategy against all types of cancer cells. We have demonstrated that arginine depletion damages mitochondrial activity, leading to chromatophagy and mitophagy in both breast and prostate cancer cells. Moreover, several recent reports have identified arginine as a critical amino acid for inducing mTORC1 signaling and it is required for aberrant growth factor-induced mTOR pathway often found in tumor cells. Together, these studies put arginine in the driver's seat for tumor cell proliferation. We will discuss whether arginine restriction deranges the mitochondrial biology, altering epigenetic modification homeostasis, whether arginine restriction plays a dual role in cancer, whether intrinsic arginine restriction facilitates tumorigenesis and external arginine restriction limits tumor progression in the context of ASS1 silencing, and will sustained arginine restriction promote irreversible chromatin modifications (chromatin closing) that cannot be reversed when arginine levels are normalized to remain unanswered. Restriction of arginine may be sufficient to sensitize many cancer cells of different tissues and genetic backgrounds to radio-/chemo-therapy.

106-03-24

The Role of Tumor Microenvironment in tumor growth and progression

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Syllabus

The hallmarks of cancer cells different from normal cells:

uncontrolled growth, resistance to apoptosis, immortal, escape immune surveillance, tumor promoting inflammation, activation of growth enhancing signaling, increased glycolysis (Warburg effect), genome instability, local and distant metastasis, angiogenesis, local and distant metastasis

Among the most challenging issues of cancer treatment:

Metastasis, recurrence, drug resistance, cancer stem cells

Important concepts of tumor development and progression:

Tumor cells orchestrate stroma cells to support their growth and survival, and together they co-evolve during tumor progression.

Angiogenesis switch (ability to attain neoangiogenesis) is a critical step that endows tumor cells the ability to progress into a large tumor.

Successful tumor progression requires overcoming hypoxia and nutritional stress, as well as evasion of immune suppression.

Tumor cells loss tissue specificity and attain ability to metastasize to distant organs.

Important issues/questions in cancer

*** Are there effective ways in daily life to reduce cancer incidence?**

diet, exercise, non-steroid anti-inflammatory drug supplement , toxin avoidance etc

*** To develop novel anti-cancer therapeutics**

novel or improved small molecule inhibitors, targeted therapy, new chemo combination, old drugs new use etc

*** How tumor microenvironment interplays with tumor cells to affect tumor progression and metastasis?**

immune surveillance, metabolism, angiogenesis, growth factors, cytokine, chemokines, extracellular matrix etc

*** What is the role of "tumor initiator" cells (tumor stem cells) in drug resistance and metastasis?**

identity, stability, plasticity, tumorigenicity, metastasis, drug screening

*** Are there effective ways to modulate tumor microenvironment to keep microscopic tumors dormant?**

immune modulation, nutrient deprivation (amino acid, carbohydrate starvation), neutralization antibodies against stroma factors

*** To develop innovative and effective drug delivery method:**

targeted specific, nanoparticles

*** Immune checkpoint therapy**

Immune modulation antibodies/agents

***How tumor microenvironment interact with cancer cells and affect their dormancy, progression, and metastasis?**

Understand the mechanism and develop effective intervening strategies

*** To develop useful animal models for studying all the above:**

tissue-specific transgenic/knockout models, zebra fish based drug screening models

Why Tumor microenvironment is important in cancer?

Cells and non-cellular constituents including matrices, growth factors and cytokines surrounding the tumor cells are referred to as stroma, or collectively called tumor microenvironment. A major conceptual change in recent year's cancer research is that the growth and progression of a tumor is not solely dependent on the genes changes that drive the behavior of tumor cells, instead, they depend greatly, if not completely, on the interaction between tumor and stroma cells and their microenvironment. Normal and neoplastic epithelial tissues are often formed from interdependent cell types, whose interaction manifest the eventual outcome of tumor cells.

Storma: organelles, cells, matrix, growth factors, cytokines

Stroma cells: Fibroblasts, Myofibroblasts, Endothelial cells, Pericytes, Smooth muscle cells, Adipocytes, Myeloid derived cells, Monocytes, Macrophages, NK. ,Dendritic ells
Lymphocytes, Mast cells etc

Non cell constituents: matrices, growth factor, cytokines

Organelles: lymphatic vessels, blood vessels, nerves

Stroma molecules relevant for tumor growth via heterotypic signaling between tumor cells and stroma cells:

Mitogenic growth factors:

HGF, PDGF, VEGF, TGF alpha

Growth inhibitors
TGF beta
Trophic (survival) factors:
IGF-1,2
Chemokines
Angiogenesis regulatory molecules

Role of stroma fibroblasts/myofibroblasts in tumor growth and progression
The cancer cells could co-evolve, educate and convert stoma fibroblasts, which originally inhibit tumor cells, to become "tumor-associated myofibroblasts" that could promote tumor cell growth, angiogenesis and metastasis. When tumor cells are mixed with myofibroblasts and injected into receptive host animal like experimental mice, they grow much faster than injecting tumor cells per se. Myofibroblasts are able to attract clustering of endothelial cells in stroma to promote neoangiogenesis, or formation of new blood vessels, needed for tumor cell growth.

Role of macrophages in tumor growth:
There are two types of macrophages, M1 and M2 with are distinctive in their cell surface markers and functions. M1 is inhibitory to tumor growth, while M2 is the opposite. Tumor cells can secrete cytokines to attract M2 gathering into tumor stroma, promote differentiation of bone-marrow-derived monocytes or granulocytes into M2, or differentiation of stroma M1 into M2. The activated macrophages are called tumor-associated macrophages (TAM), which represent important participants in enhancing angiogenesis and metastasis.

Role of other immune cells in tumor growth:
Aside from macrophages, there are several other immune cells know to be important in regulating tumor growth. Dendritic and NK cells are tumor suppressive, and so are CD4 and CD8 positive T cells. Whereas marrow-derive suppressive cells (MDSCs) and regulatory T cells (Treg) are tumor promoting. The distribution of pro- and anti-tumor immune cells in stroma depend on the types of cytokines produced by tumor cells and their surrounding immune cells. The dynamic landscape of the immune cells in tumor microenvironment determines the status of tumor growth or inhibition. And this could be affected by inflammatory status of the host and at the tumor site.

How do we study tumor microenvironment?
Some examples:
1. Employ transgenic or xenograft mouse models to study the evolution of stroma

during tumor growth. IHC can be used to identify the presence and distribution of various immune cells and cytokines.

2. Isolation of specific stroma cells using laser-capture dissection or cell sorting to study the changes of tumor microenvironment during tumor progression from defined clinical samples or from experimental tumor models

3. Isolation of isogenic pairs of low and high metastatic cancer cell lines to compare the distinct stroma-tumor cell interaction and the distribution of cytokines and immune cells in tumor microenvironment. cDNA array and metabolomics analysis can also be used.

4. 3-D imaging with specific labeling of cells or matrix molecules of tumor stroma during tumor development

5. Using specific transgenic or knock out mouse models or specific immune cell neutralization antibodies to study the distribution of immune cells in stroma versus the tumor progression and metastasis.

106-03-31

SUMOylation of XRCC1 activated by poly(ADP-ribosyl)ation regulates DNA repair

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Abstract

Base excision repair (BER) fixes DNA base lesions and single-strand breaks (SSBs), which are caused by ubiquitous endogenous and exogenous agents, including reactive oxygen species, alkylating agents, and ionizing irradiation. Impaired BER results in both a decreased cellular capacity to counter genotoxic stress and increased genomic instability. BER is initiated by excision of the damaged base by DNA glycosylases and subsequently leads to a SSB, which is then filled by DNA polymerase β (POLB) and DNA ligase III (LIG3). When SSBs are formed, the DNA-damage response (DDR) is activated to promote efficient BER via phosphorylation of the BER proteins by ATM/ATR-associated signals and poly(ADP-ribosyl)ation (PARylation) of multiple BER proteins by poly(ADP-ribose) polymerase (PARP). XRCC1 plays a central role in BER, and its loss in cells leads to increased chromosomal instability and impaired DNA repair. XRCC1 itself has no enzymatic activity, but the scaffold function of XRCC1 is essential for BER. XRCC1 specifically interacts with other BER components through different domains: the N-terminal domain (NTD) interacts with POLB, the BRCA1 C-terminal (BRCT) I domain interacts with PAR, and the BRCT II domain interacts with LIG. Therefore, we wished to identify the regulatory mechanisms that control XRCC1 interactions with other BER components. Here we show that SUMOylation of XRCC1 is regulated in cells under methyl-methanesulfonate (MMS) treatment and is critical for BER. In response to MMS treatment, poly(ADP-ribose) polymerase (PARP) is activated immediately and synthesizes poly(ADP-ribose) (PAR), which in turn promotes recruitment of SUMO E3 TOPORS to XRCC1 and facilitates XRCC1 SUMOylation. A SUMOylation-defective mutant of XRCC1 had lower binding activity for the BER protein DNA polymerase beta (POLB) and was linked to a lower capacity for repair of MMS-induced DNA damages. Our study therefore identified a pathway in which DNA damage-induced poly(ADP-ribosyl)ation (PARylation) promotes SUMOylation of XRCC1, which leads to more efficient recruitment of POLB to complete BER.

106-04-07

Endocrine Disrupting Chemicals: Perfluoroalkyl Substances

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Abstract

Perfluoroalkyl substances (PFASs), one class of endocrine disrupting chemicals, consist of a backbone typically 4 to 14 carbons in length and a charged function moiety. These compounds have been used in a variety of consumer and industrial applications since 1950. Health concerns for PFASs include hepatotoxicity, developmental toxicity, immunotoxicity, hormone disturbances, and tumorigenic potential. Our data from the Taiwan Birth Panel Study suggest inverse associations between perfluorooctane sulfate (PFOS) levels in umbilical cord blood plasma and birth outcomes and gross and fine motor development. Prenatal PFOS and perfluorooctanoic acid (PFOA) exposures positively correlated with cord blood IgE levels. In the Genetic and Biomarkers study for Childhood Asthma, we found that positive associations between serum PFASs and asthma, and positive associations between PFASs and IgE, absolute eosinophil counts (AEC), and eosinophilic cationic protein (ECP) levels, and asthma severity scores in asthmatic children. In the Taiwan Adolescent Panel Study, higher serum concentrations of PFOS were associated with an increase of carotid artery intima-media thickness in adolescents and young adults. In conclusion, exposure to lower levels of PFASs can pose significant hazards to children's health. Mechanistic research is needed to elucidate causal relations.

106-04-21

Stem Cells for Tissue Regeneration in Dentistry

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Abstract

Due to the development of regenerative medicine, the application of stem cells, growth factors and biomaterials for tissue regeneration had been widely investigated. There are many researchers interested in tooth regeneration and salivary gland regeneration. In our studies for tooth regeneration, tooth regeneration with complete root formation including dental pulp, dentin, cementum and periodontal ligaments in mini pigs was demonstrated by isolating and loading the tooth germ cells in gelatin-chondroitin-hyaluronan-tri-copolymer scaffolds. In addition, the interactions of tooth germ cells with biomaterials had also been investigated. Neural differentiation of dental pulp stem cells is also possible for further clinical applications.

For salivary gland regeneration, long term culture system of acinar cells with functional expression had been established in our laboratory. Interactions between acinar cells and biomaterials had also been demonstrated. In our studies, bone marrow mesenchymal stem cells (BMMSCs) were able to be transdifferentiated into acinar like cells both in vitro and in vivo. By using irradiated mice as animal model and application of nanoparticles for labeling of BMMSCs, transdifferentiation of BMMSCs into acinar like cells are able to be displayed and applied for salivary gland regeneration. The results indicated that by transplantation of bone marrow stem cells or acinar like cells into the irradiated mice with damaged salivary glands, the body weight, glands weight and saliva production of the mice were shown to be increased and closed to normal control. It was found that cell therapy with BMMSCs for salivary gland regeneration is possible.

Conclusion: Both tooth regeneration and salivary gland regeneration are possible and it is worthy for further study and developing for clinical applications.

Key words: tooth regeneration, salivary glands regeneration,
bone marrow mesenchymal stem cells, transdifferentiation, biomaterials

106-04-28

Human Pluripotent Stem Cells in Cardiac Regeneration: the Promise and Challenges for Clinical Translation

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Abstract

Cardiovascular diseases, especially ischemic heart disease, plague worldwide. Myocardial ischemia will cause loss of cardiomyocytes, leading to heart failure. Despite significant advances in modern medical and surgical therapy, cardiovascular disease is still the top one leading cause of death. Thus, a robust therapy to regenerate myocardium should help millions of patients every year. Notwithstanding that heart regeneration has been well documented in amphibia, fish and developing mammals, the ability of regeneration in human heart is limited. In recent two decades, the field of heart regeneration has emerged from a far-fetch idea to the forefront of cardiac research. Several strategies to remuscularize the injured heart using adult stem cells and pluripotent stem cells, cellular repro¬gramming and tissue engineering are in progress. Additionally, several stem cell clinical trials have been investigated and the results are either marginally successful or neutral. Although many translational challenges remain, exciting step has been made to establish stem cell therapy techniques in recent years, and new preclinical studies in large animal models have shed light on the promises and challenges that lie ahead. Nevertheless, we have to acknowledge that there are many critical challenges facing clinical translation.

106-05-05

Using Mouse Genetic Models to Dissect Developmental Defects in Neurological Disorders

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Abstract

My team has been aiming to elucidate how neurons differentiate their crucial subcellular structures, including synapses, dendrites and axons, to achieve the function of receiving and delivering signals among neurons. Because appropriate neurodevelopment is essential for neural function, it is not surprising that the genes regulating neural development are associated with neurological diseases, particularly neurodevelopmental disorders. To further elucidate the molecular etiology of neurodevelopmental disorders, in addition to neuronal morphology, we have also extended our study to mouse behavior analyses, particularly those related to autism-like behaviors, and circuit characterization using tracing approaches. Our studies have revealed the detailed molecular regulation of neural development, as well as the molecular etiology of several neurological disorders. Our most recent research studies about autism spectrum disorders will be reported in the meeting.

106-05-12

Discovery and Development of Anticancer Agents on Natural Products – Difficulties and Opportunities

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Abstract

Malignancy is the leading cause of death in a lot of countries. Our lab has been working on preclinical development of anticancer agents. We have established a screening system, sulforhodamine B assay (SRB assay), according to National Cancer Institute in USA and have been doing a large scale of screening tests to discover potential agents against cancers. In recent decade, we have screened more than 7000 samples from both chemically synthetic compounds and natural products. The mechanisms of anticancer abilities of the effective compounds were studied. Several natural products will be focused in this presentation. The first is cryptocaryone, a natural dihydrochalcone. Several pharmacological and biochemical assays were used to characterize the apoptotic signaling pathways of cryptocaryone in prostate cancer cells. The data suggest that cryptocaryone displays anticancer activity through the stimulation of death receptor and associated molecule clustering, leading to caspase-8 and 3 activation, and apoptosis. The next is reevesioside series of compounds, including Reevesioside A, Reevesioside F and Epi-reevesioside F provided by professor Ih-Sheng Chen (Kaohsiung Medical University). The data suggest that the reevesioside compound inhibits c-myc expression and down-regulates the expression of CDC25A, cyclin D1 and cyclin E, leading to a profound decrease of RB phosphorylation. G1 arrest is, therefore, induced through E2F1 suppression. Consequently, reevesioside A causes mitochondrial damage and an ultimate apoptosis in human hormone-refractory prostate cancer cells. Interestingly, these compounds induce anticancer activities through different signaling pathways in different types of cancer cells. They induce apoptosis through the down-regulation of survivin and Mcl-1, and the formation of pro-apoptotic fragments from Bcl-2 family members in leukemic cells. The loss of $\Delta\Psi m$ and mitochondrial damage are responsible for the activation of caspases. Moreover, the amplification of caspase-3-mediated signaling pathway contributes largely to the execution of apoptosis. After the identification of potential compound candidates, a variety of derivatives that may have better PKs, solubility and efficacies, and less toxicities can be obtained for further development.

106-05-19

The Tao of integuments and its application

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Abstract

Integument form the interface between an organism and its environment, to serve the function of defense, communication, endothermy, etc. The integument serves diverse functions including barrier, communication, endothermy, defense, etc. and is adaptive to changing environments. It is instructive to consider nature's way of integumentary organ design - the Tao of the integuments, that can accommodate such complexity. 1) Periodic pattern formation. It evolved as an effective design that helps animals heal better after wounding and to generate combinatorial complexity. This is achieved by partitioning the integument into numerous elements (> 30,000 hair or feather follicles in mice or bird). 2) Stem cell based cyclic renewal of each element. Each appendage element, now has its own stem cells and is regulated differently for its growth phase and resting phase. Length of a hair or feather is proportional to the duration of the growth phase, thus forms the long terminal scalp hairs and the short villus facial hairs. 3) Regional specific appendage phenotypes. For best adaptation, different body regions evolve different appendage phenotypes (e.g., downy, flight, and contour feathers), which are modulated by mesenchymal signals, body hormone status, seasons, and aging. 4) Novel collective regenerative behaviors. These includes the communication among hair follicles in a population, interaction with immune system (e.g., quorum sensing of hair regeneration), neural input, etc.

Toward application, we can use nature's way to modulate each of the above organization principle. We can identify communication cytokines that facilitate or suppress hair regeneration. We can identify hormone pathways or dermal factors that modulate hair follicle cyclic regenerative behavior in aging or androgenetic alopecia. To manage burn and other sever wounding situations, we can elicit self-organizing periodic pattering process to generate reconstituted skin with hairs in the context of tissue engineering. Thus, nature inspired regenerative principles help us make progress toward regenerative medicine.

Overview:
Lai, Y. C., Chuong, C. M. 2016. The "Tao" of integuments. Science. 354:1533-1534.
Lei, M and Chuong, CM. 2016. Aging, alopecia and stem cells. Science. 351: 559-560.
Widelitz, R. and Chuong, C.M. 2016. Quorum sensing and other collective regenerative behavior in organ populations. Curr Opin in Genetics and Develop. 40:138-143.

Research articles:
Li, A., Figueroa, S., Jiang, T. X., Ping, W., Widelitz, R., Nie, Q., Chuong, C. M. 2017, Diverse feather shape evolution made possible by anisotropic mesenchymal signaling modules. Nature Communications. In press.
Chen, C. C., Wang, L., Plikus, M. V., Jiang, T. X., Murray, P. J., Ramos, R., Guerrero-Juarez, C. F., Hughes, M. W., Lee, O. K., Shi, S. T., Widelitz, R. B., Lander, A. D., Chuong, C. M. 2015. Organ-level quorum sensing directs regeneration in hair stem cell populations. Cell, 161:277-290.
Lee, L. F., Jiang, T. X., Garner, W., Chuong, C. M. 2011. A simplified procedure to reconstitute hair-producing skin. Tissue Eng Part C-Methods, 17:391-400.

106-05-26

Potential Plasma Biomarkers for Nonalcoholic Fatty Liver Disease and nutritional regulation of the disease

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Abstract

Background: Prevalent worldwide obesity is associated with increased incidence of nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome. The identification of noninvasive biomarkers for NAFLD is of recent interest. Because primary de novo lipogenesis occurs in chicken liver as in human liver, adult chickens with age-associated steatosis resembling human NAFLD is an appealing animal model. Objective: The objective of this study was to screen potential biomarkers in the chicken model for NAFLD by transcriptomic and proteomic analysis. Methods: Hy-Line laying hens were fed standard feed from 25 to 45 wk of age to induce fatty liver. They were killed every 4 wk and liver and plasma were collected at each time point to assess fatty liver development and for transcriptomic and proteomic analysis. Next, selected biomarkers were confirmed in additional experiments by providing supplements of the hepatoprotective nutrients betaine [300, 600, or 900 partspermillion (ppm) in vivo; 2mM in vitro] or docosahexaenoic acid (DHA; 1% in vivo; 100 mM in vitro) to 30-wk-old Hy-Line W-36 laying hens for 4 mo and to Hy-Line W-36 chicken primary hepatocytes with oleic acid–induced steatosis. Liver or hepatocyte lipid contents and the expression of biomarkers were then examined. Results: Plasma acetoacetyl-CoA synthetase (AACS), dipeptidyl-peptidase 4 (DPP4), glutamine synthetase (GLUL), and glutathione S-transferase (GST) concentrations are well-established biomarkers for NAFLD. Selected biomarkers had significant positive associations with hepatic lipid deposition ($P < 0.001$). Betaine (900 ppm in vivo; 2 mM in vitro) and DHA (1% in vivo; 100 mM in vitro) supplementation both resulted in lower steatosis accompanied by the reduced expression of selected biomarkers in vivo and in vitro ($P < 0.05$). Conclusion: This study used adult laying hens to identify biomarkers for NAFLD and indicated that AACS, DPP4, GLUL, and GST could be considered to be potential diagnostic indicators for NAFLD in the future.

106-06-02

Hyaluronate-Based Thermo-sensitive Hydrogel as Cell Carrier for Nucleus Pulposus Regeneration and Vitreous Body Substitute

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Abstract

Intervertebral disc degeneration usually starts at the nucleus pulposus. In the past decades, several techniques and prosthetics (artificial disc) have been developed to regenerate or replace the nucleus pulposus. However, these kind of pre-formed devices have to remove the nucleus pulposus and then replace an artificial one to relief the symptom of intervertebral disc degeneration. Recently, cell-based tissue engineering provides a rational approach to regenerate active nucleus pulposus cells (NP cells) to restore intervertebral disc architecture and function. However, the source of autologous nucleus pulposus cells are limited and their functional state does not favor regeneration. Besides, nucleus pulposus cells grown in monolayer may result in fibroblast-like transformation. Thus, the 3D hydrogel co-culture system maybe an alternative method to provide an adequate environment for nucleus pulposus cells proliferation, extracellular matrix production, cytokines secretion.

Human vitreous is a gelatinous substance that is predominantly composed of collagen fibril, hyaluronic acid (HA) and water (97–99%). Vitreous substitutes are needed to tamponade the detached retina after vitrectomy when treating retinal detachments. However, several drawbacks associated with current vitreous substitutes have been reported. In the present study, we developed a colorless, transparent and injectable hydrogel as a vitreous substitute that was formed by oxidated HA (oxi-HA) and adipic acid dihydrazide (ADH). The results of biodegradation demonstrated that the hydrogel could maintain its gel matrix over at least 35 days depending on the ADH concentration. In addition, the biocompatibility was evaluated on a retina pigmented epithelium (RPE) cell culture following ISO 10993-5 (tests for in vitro cytotoxicity), and the hydrogel was found to be nontoxic. This study suggested that the injectable oxi-HA/ADH hydrogel could fulfill many critical elements that are desirable in vitreous substitutes.