一般論文壁報發表 Poster Presentation

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類別	編號
Basic	B001 – B018
Clinical	C001 – C198

基礎研究組壁報發表 Basic Poster

【Basic】

B001-B018　Chair(s)：賴俊夫/ Chun-Fu Lai、吳建興/ Chien-Hsing Wu

B001 Discoidin Domain-Containing Receptor 2 in Pericyte Plays a Crucial Role in AKI-CKD Continuum

Hui-Chiun Tseng[1], Yu-Hsiang Chou[2], Shuei-Liong Lin[1,2]

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B002 The Ameliorative Effect of Desmethoxykhellin on Septic Acute Kidney Injury Via SLC7A11/GPX4 Inactivation-Mediated Ferroptosis Pathway

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B003 Albumin Induces Epithelial-Mesenchymal Transition Via Cross-Talk between ROS and ER Stress in Podocytess

白蛋白藉由活性氧類和內質網壓力交互作用來引發腎絲球足細胞的上皮間葉轉換

Chien-An Chen[1], Jer-Ming Chang[2], Hung-Chun Chen[2], Eddy-Essen Chang[2]

陳建安[1], 張哲銘[2], 陳鴻鈞[2], 張一旋[2]

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B004 Gut Flora Metagenomic Analysis Coupled with Metabolic and Deep Immune Profiling in Chronic Kidney Disease

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B005 5-Methoxytryptophan Protects Against Toll-Like Receptor 2 Mediated Renal Tissue Inflammation and Fibrosis in A Murine Unilateral Ureteral Obstruction Model
5-甲氧基色氨酸在小鼠單側輸尿管阻塞模型中預防類鐸受體 2 介導的腎臟發炎和纖維化
Ryan Chen[1] and Jing-Yiing Wu[2], Guan-Lin Lee2, Yu-Fan Chueh[2], Cheng-Chin Kuo[2], Kenneth K Wu[2], Yu-Juei Hsu[3,4]
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B006 Beta-Mangostin Alleviates Renal Tubulointerstitial Fibrosis Via TGF-β1/JNK Signal-ing Pathway
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B007 Discovery of Novel Drugs as Ddrs Kinase Inhibitors for Preventing Chronic Kidney Disease
開發新穎的盤基蛋白激酶之抑制藥物用於預防慢性腎臟病
Hui-Wen Chiu [1,2], Hung-Jin Huang [1], Yen-Chung Lin [3,4]
邱惠雯 [1,2], 黃泓縉 [1], 林彥仲 [3,4]
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B008 Single-Cell and Spatial Transcriptome Analyses Reveal Coordinated Metabolic and Inflammatory Changes of Blood-Gut-Kidney Tissues Linked to Improvement of Microalbuminuria After Oral Bacteroid Spp Treatment in Mouse Models
I-Wen Wu[1], Shih-Chi Su[2], Lun-Ching Chang[3], Mai-Szu Wu[4]
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黏著斑激酶訊號傳導調度小鼠腎上皮細胞內功能性水通道蛋白的定位
I-Ching Kuo[1,2,3], Yen-Yi Zhen[2], Chi-Chih Hung[2], Yi-Wen Chiu[2]
郭宜瑾 [1,2,3], 陳晏裕 [2], 洪啟智 [2], 邱怡文 [2]
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B011 Restoration of Mitophagy in Osteocytes by AST-120 Improves Bone Phenotype in a 5/6 Nephrectomy Mouse Model of Chronic Kidney Disease
AST-120 通過恢復骨細胞粒線體自噬功能改善 5/6 腎切除小鼠模型骨病變
Wyatt Hsieh[1] and Tsung-Han Lin[2], Cheng Wen Hsu[2], Chun-Liang Hsu[3], Shun-Neng Hsu[2] and Yu-Juei Hsu[2, 4]
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B012 Bitter Melon and Chlorella Extract Complexes may Have Effects on Improving Metabolism Syndromes
山苦瓜與螺旋藻萃取複合物可能具改善血糖及脂質代謝症候群之功效
Jui-Ting Chang[1, 2, 3], Pai-Lung Chou[4], Yu-Chuan Tsai[5], Yin-Syuan Huang[5], Ya-Syuan Wu5, Guan-Pin Su[5], Jiunn-Jye Chuu[5]
張瑞廷 [1,2,3], 周佰隆 [4], 蔡鈺絹 [5], 黃尹萱 [5], 吳亜瑄 [5], 蘇冠頻 [5], 褚俊傑 [5]
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B013 Single-Cell RNAseq Analysis Reveals Immune landscape in Peritoneal Dialysis Fluid
單細胞 RNA 測序分析揭示腹膜透析液中的免疫圖譜
Siao Muk Cheng[1], Chih-Chuan Yu[1], An-Fu Lee[1], Chi-Yen Chang[1], Daw-Yang Hwang [1,2] and Yi-Wen Chiu[2]
鍾校木 [1], 余智娟 [1], 李安富 [1], 張琦豔 [1], 黃道揚 [1,2], 邱怡文 [2]
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B14 Two New Histone Deacetylase Inhibitors for Bladder Cancer Therapy
兩種具膀胱癌療效的新型組蛋白去乙醯酶抑制劑
Shou-Chieh Wang[1], Yi-Wen Liu[2], Cheng-Huang Shen[3], Hsin-Ting Liu[2]
王守玠 [1], 劉怡文 [2], 沈正煌 [3], 劉欣婷 [2]
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B015 Indoxyl Sulfate is Associated with Cognitive Impairment in Esrd Patients by Activating the Extrinsic Apoptosis in the Neuronal Cells During Differentiating Process
硫酸吲哚酚藉由活化分化中神經細胞之外源性凋亡造成末期腎病病患認知障礙的相關性研究
Yi-Chou Hou[1], Kuo-Cheng Lu[2], Cheung-Lin Huang[3], Jiun-Jie Wang[4], Ruei-Ming Chen[5], Yuahn-Sieh Huang[6]
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B016 The Essential Role of O-Antigen in Uropathogenic E. coli-Induced Neutrophil Extracellular Trap Formation

O 抗原在泌尿道致病性大腸桿菌誘導的嗜中性細胞胞外誘捕網形成中的重要作用

Wei-Hung Lin[1], Jo-Yen Chao[1], Ching-Hao Teng[2], Tzu-Shan Huang[1], Wei-Ren Lin[1], Chin-Chung Tseng[1], Ming-Cheng Wang[1,3]

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B017 Effects of SGLT2 Inhibitors on Modulating Protein-Bound Uremic Toxins and Gut Microbiota in Pre-Dialysis Chronic Kidney Disease Patients: A Matched Case-Control Study

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B018 Long-Term Proteomic Changes from Human Urinary Extracellular Vesicles in Diabetic Patients After Administrating SGLT2 Inhibitors

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張心儀[1], 羅以筑[2],蔡宜純[3], 陳敏修[1,2], 許育瑞[2], 林石化[2], 宋志建[2]

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B001

Discoidin Domain-containing Receptor 2 in pericyte plays a crucial role in AKI-CKD continuum

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Background:

Acute kidney injury (AKI) is a major cause of chronic kidney disease (CKD). Mechanisms of AKI-to-CKD continuum needs to be further investigated for the development of promising pharmacologic agents. Discoidin domain recepors (DDRs) including DDR1 and DDR2, which are receptor tyrosine kinases that bind to and activated by collagen in the extracellular matrix (ECM). While the role of function of DDR2 in the process of AKI-CKD continuum is less clearly understood.

Methods:

We evaluated the DDR2 expression in the whole kidney and isolated pericytes during AKI-CKD continuum. We used collagen 1 as DDR2 stimulator and WRG-28 as DDR2 inhibitor in the NIH/3T3 and C3H10T cells to measure the expression level of fibrosis-related genes and proteins in these cell lines.

Results:

Our results demonstrated that DDR2 is expressed mainly in pericytes. DDR2 expression increased in the whole kidney and isolated pericytes during AKI-CKD continuum. In experiments of cell lines, 200 μg/ml of collagen-1 treatment for 4 hours could activate the fibrosis-related genes. In addition, DDR2 inhibitor, WRG-28 impeded collagen-1-induced DDR2 activity and fibrosis-related gene expression levels.

Conclusions:

DDR2 expresses in pericytes and increased during AKI-CKD continuum. *In vitro,* collagen 1 activates DDR2 and promotes pro-fibrotic genes in pericytes. Inhibition of DDR2 ameliorates pericytes activity and collagen production. The *in vivo* effect of pericyte-specific DDR2 knockout on AKI-to-CKD in under study. Current data supports that regulation of the DDR2 is a crucial factor for the therapeutic strategy for AKI-to-CKD continuum.

Key words: AKI-CKD continuum, DDR2, pericyte

B002

The ameliorative effect of Desmethoxykhellin on septic acute kidney injury via SLC7A11/GPX4 inactivation-mediated ferroptosis pathway

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Background: Oxidative stress plays a pivotal role in the progression of septic acute kidney injury (S-AKI). This oxidative imbalance can trigger ferroptosis and the SLC7A11/GPX4 pathway is central to the regulation of ferroptosis by inhibition of lipid peroxidation. Desmethoxykhellin, with bioactive properties, including anti-inflammatory, antioxidant, and vasodilatory effects, could serve as a potential candidate in the development of treatments.

Methods: S-AKI animal model was induced by endotoxin in BALB/c mice. Kidney pathology was assessed to observe the protective effects of desmethoxykhellin against kidney injury. Lipid peroxidation, ironic accumulation and antioxidative enzymes (GSH, SOD and catalase) were assessed by commercial assay kits. Ferroptosis pathway related proteins were detected by western blot.

Results: Desmethoxykhellin improved septic-AKI by reducing cellular necrosis, apoptosis, the loss of brush border in renal tubules, interstitial edema, vacuolization, renal tubular dilation, and glomerular cavity shrinkage. It reduced endotoxin-induced lipid peroxidation and enhance the activity of antioxidative enzymes (GSH, SOD, and catalase). Desmethoxykhellind also regulated endotoxin-induced ferroptosis-related proteins, including SLC7A11, SLC3A2, GPX4, and ACSL4.

Conclusions: Desmethoxykhellin effectively ameliorates septic AKI via SLC7A11/GPX4 inactivation-mediated ferroptosis pathway in BALB/c mouse model. Further investigation is needed to clarify its clinical applications.

Key words: Septic acute kidney injury, Desmethoxykhellin, antioxidative system, Ferroptosis, SLC7A11/GPX4 signaling pathway

B003

Albumin induces epithelial-mesenchymal transition via cross-talk between ROS and ER stress in podocytess

白蛋白藉由活性氧類和內質網壓力交互作用來引發腎絲球足細胞的上皮間葉轉換

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Background: albuminuria is associated with progresson of chronic kidney disease. Epithelial-mesenchymal transition (EMT) plays a significant role in cell migration and fibrosis. Podocyte may undergo EMT after injury, leading to podocyte migration and detachment that ultimately leads to defective glomerular filtration. The endoplasmic reticulum (ER) and reactive oxygen species (ROS) play a major role in EMT. The pathophysiology linking albuminuria to progression of renal function is complex and still incompletely understood. In this study, we evaluate whether albuminuria induces ROS and ER stress that cause EMT.

Methods: Podocytes were exposed to medium alone or in high concentrations of delipidated, endotoxin-free human serum albumin (HSA, 10 mg/ml) with or without antioxidant and ER stress inhibitors. Intracellular reactive oxygen species (ROS) generation was estimated with fluorescent indicator 20,70-dichlorofluorescin diacetate (DCF-DA). The mRNA and protein expression of α-SMA (EMT biomarker) and ER stress biomarkers were measured by real-time PCR and Western blotting.

Results: The endocytosis of HSA by podocyte was found after HSA treatment. The intracellular ROS production was increased after HSA treatment. The biomarkers of ER stress (GRP78 and CHOP) were up-regulated at 48 h after HSA treatment and were down-regulated after NAC (antioxidant) + HSA treatment. HSA induced mRNA and protein expression of α-SMA. The ER stress inhibitors (4-PBA and Sal) and NAC attenuated the HSA-induced mRNA and protein expression of α-SMA. Intracellular ROS production induced by HSA was down-regulated after NAC treatment.

Conclusion: Albuminuria induces EMT of podocyte through crosstalk between ROS and ER stress. This may lead podocytes to secreting pro-fibrotic cytokines, migration and detachment that promote progression of albuminuria and glomerulosclerosis.

Keywords: albuminuria, epithelial-mesenchymal transition, ROS, ER stress

B004

Gut flora metagenomic analysis coupled with metabolic and deep immune profiling in chronic kidney disease

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Background:
Perturbation of gut microbiota has been linked to chronic kidney disease (CKD), which was correlated with a sophisticated milieu of metabolic and immune dysregulation.
Methods:
To clarify the underlying host–microbe interaction in CKD, we performed multi-omics measurements, including systems-level gut microbiome, targeted serum metabolome and deep immunotyping, in a cohort of patients and non-CKD controls.
Results:
Our analyses on functional profiles of the gut microbiome showed a decrease in the diversity and abundance of carbohydrate-active enzyme (CAZyme) genes but an increase in the abundance of antibiotic resistance, nitrogen cycling enzyme and virulence factor genes in CKD. Moreover, models generated using measurements of serum metabolites (amino acids, bile acids and short-chain fatty acids) or immunotypes were predictive of renal impairment but less so than many of the functional profiles derived from gut microbiota, with the CAZyme genes being the top-performing model to accurately predict the early stage of diseases. In addition, co-occurrence analyses revealed coordinated host–microbe relationships in CKD. Specifically, the highest fractions of significant correlations were identified with circulating metabolites by several taxonomic and functional profiles of gut microbiome, while immunotype features were moderately associated with the abundance of microbiome-encoded metabolic pathways and serum levels of amino acids (e.g. B cell cluster tryptophan and B cell cluster tryptophan metabolism).
Conclusions:
Overall, our multi-omics integration revealed several signatures of systems-level gut microbiome in robust associations with host–microbe co-metabolites and renal function, which may have etiological and diagnostic implications in CKD.
Key words:
Carbohydrate-active enzyme, chronic kidney disease, gut microbiome, immunotype, metabolite

B005

5-methoxytryptophan protects against toll-like receptor 2 mediated renal tissue inflammation and fibrosis in a murine unilateral ureteral obstruction model

5-甲氧基色氨酸在小鼠單側輸尿管阻塞模型中預防類鐸受體 2 介導的腎臟發炎和纖維化

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Background: 5-methoxytryptophan (5-MTP) is a cellular metabolite with anti-inflammatory properties. Several recent reports indicate that 5-MTP protects against post-injury tissue fibrosis. It was unclear how 5-MTP controls tissue fibrosis. We postulated that 5-MTP attenuates renal interstitial fibrosis by blocking toll-like receptor 2 (TLR2) and transforming growth factor β (TGFβ) signaling pathways.

Methods: In vivo experiments were carried out in a well-established UUO model in wild-type (WT) and $tlr2^{-/-}$ mice. The effect of 5-MTP on renal fibrosis was evaluated by pretreatment of WT UUO mice with intraperitoneal administration of 5-MTP. To determine whether 5-MTP attenuates fibrosis by inhibiting TLR2 and TGFβ signaling pathways, we evaluated the effect of 5-MTP on TLR2-induced fibroblast phenotypic switch in NRK-49F fibroblasts and TLR2 and TGFβ signaling pathways in human proximal tubular epithelial cells (HPTEC) and RAW264.7 macrophages stimulated with Pam3CSK4 (Pam3) or TGFβ1.

Results: UUO-induced renal fibrosis was abrogated in $tlr2^{-/-}$mice, consistent with a crucial role of TLR2 in UUO-induced renal fibrosis. UUO-induced macrophage infiltration and pro-fibrotic cytokine production in renal tissues were suppressed by tlr2 knockout. 5-MTP administration attenuated renal tissue fibrosis accompanied by a reduction of macrophage infiltration and IL-6 and TGFβ levels. 5-MTP inhibits TLR2 upregulation and blocks TLR2-MyD88-TRAF6 signaling pathway in macrophages. Furthermore, 5-MTP blocked the Pam3- and TGFβ1-induced phenotypic switch of NRK-49F to myofibroblasts and inhibited Pam3- and TGFβ1-induced signaling pathways in HPTECs and RAW264.7 cells.

Conclusions: 5-MTP is effective in protecting against UUO-induced renal interstitial fibrosis by blocking TLR2 and TGFβ signaling pathways.

Keywords: 5-methoxytryptophan, Toll-like receptor 2, renal fibrosis, unilateral ureteral obstruction, p38 MAPK, Smad2

B006

Beta-mangostin alleviates renal tubulointerstitial fibrosis via TGF-β1/JNK signal-ing pathway

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Background

The epithelial-to-mesenchymal transition (EMT) plays a key role in the pathogenesis of kidney fibrosis, and kidney fibrosis is associated with adverse renal prognosis. Beta-mangostin (β-Mag) is a xanthone derivative from the fruit mangosteen and involved in anti-fibrotic and anti-oxidation effect. The purpose was to examine the effects and mechanisms of β-Mag on renal tubulointerstitial fibrosis both in vivo and in vitro.

Method

This study used an in vivo unilateral ureteral obstruction (UUO) model and in vitro with HK-2 cell lines treated with β-Mag and transforming growth factor β1 (TGF-β1). The expression of epithelial-mesenchymal transition (EMT)-related proteins of UUO mice was examined using western blotting, qRT-PCR and immunohistochemical staining. Cell growth and motility were evaluated using MTT and wound healing assay. Molecular mechanism was performed with Knockdown assay.

Results

From the in vivo study on the unilateral ureteral obstruction mouse model, oral β-Mag administration, in a dose-dependent manner, caused lesser degree of tubulointerstitial damage, diminished collagen I fiber deposition, and depressed expression of fibrotic markers and EMT markers in the UUO-kidney tissues. β-Mag co-treated with TGF-β1, decreased the cell motility, downregulated the EMT and phosphoryl-JNK1/2/smad2 expression. Furthermore, β-Mag co-treated with SB (smad2 kinase inhibitor) or SP600125 (JNK kinase inhibitor) significantly inhibited the TGF-β1–associated downstream phosphorylation and activation of smad2-mediated JNK1/2 tar-geting snail/Vimentin axis.

Conclusions

β-Mag protects against EMT and kidney fibrotic processes by mediating the TGF-β1/smad2/JNK targeting snail-mediated Vimentin expression and may have therapeutic implications in renal tubulointerstitial fibrosis

Key words: β-mangostin; Renal tubulointerstitial fibrosis; EMT; TGF-β1; smad2; JNK1/2

B007

Discovery of novel drugs as DDRs kinase inhibitors for preventing chronic kidney disease

開發新穎的盤基蛋白激酶之抑制藥物用於預防慢性腎臟病

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Background:
Inflammation and fibrosis are usually correlated with the leading cause of kidney failure and the progression of chronic kidney disease (CKD). However, the molecular mechanism of inflammation in the pathogenesis of CKD has not yet been fully understood. Activation of discoidin domain receptors (DDRs) induces inflammatory response and organ dysfunction has been shown to stop the repair process in fibrotic kidneys. The present study is aimed to discover novel clinically used drugs as inhibitors to block DDR activation.

Methods:
The precise type of target protein related to CKD was evaluated using mRNA levels analysis and bioinformatics to study the correlation of gene expression data in regular and CKD mice. The drugs from the database target for DDR protein were filtered using virtual screening and quantitative structure-activity relationships (QSARs) prediction model. The conformational dynamics of protein-ligand complexes were executed by molecular dynamic (MD) simulation in a supercomputer device.

Results:
The mRNA levels analysis revealed that the type 2 DDR is significantly related to the CKD mice model. In addition, the database virtual screening of precise target protein and QSAR prediction model discovered that the potential candidates have high affinities with predicted inhibitory effects from preliminary filtration. The MD simulation displayed that our candidate drug remains bound to the active site under dynamic conditions.

Conclusion:
This research revealed that the candidate drugs might have potential nephroprotective impacts that reduce the activation of the target protein. Our findings showed a new therapeutic strategy to delay CKD progression by targeting type 2 DDR, which may help the development of possible therapeutic drugs to prevent kidney-related problems in the future.

Key words:
Chronic kidney disease; QSAR; Virtual screening; Molecular dynamics; Drug repurposing

B008

Single-cell and spatial transcriptome analyses reveal coordinated metabolic and inflammatory changes of blood-gut-kidney tissues linked to improvement of microalbuminuria after oral Bacteroid spp treatment in mouse models

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Background：

Gut dysbiosis is present in chronic kidney disease (CKD) patients. Gut microbiota manipulation represents a novel and promising therapeutic approach to tackle the gut-kidney interaction. However, the candidate live bioproducts and the pathophysiology linked to its renoprotective effects remain obscure in CKD.

Methods：

Feces of 228 (16S rRNA sequencing, discovery cohort) and 93 (shotgun metagenomic sequencing, validation cohort) CKD patients were collected to evaluate candidate compounds of live biotherapeutic products for CKD treatments. Bacteroids spp were retrieved as the most discriminatory taxa associated with CKD. Clinical isolates of Bacteroid spp were retrieved from 10 health volunteers. High-fat diet (HFD,mimicking mild CKD) and adenine (mimicking moderate CKD) models were used to elucidate the causal relationship of such bacterial candidates. Microbiome, metabolome as well as single-cell and spatial transcriptome analyses were conducted to elucidate the pathophysiology of gut-kidney interaction after Bacteroids spp feeding.

Results：

We showed that colonization of Bacteroid spp in both HFD and adenine-induced mouse models of CKD by oral gavage ameliorated the morphological (podocyte foot process effacement) and functional changes (microalbuminuria levels) in the kidney. Metabolically, improvements of levels of glucose, cholesterol, TNF-$\boldsymbol{\alpha}$, IL-1$\boldsymbol{\alpha}$, IL-1$\boldsymbol{\beta}$ were seen. Single-cell and spatial transcriptomic sequencing analyses revealed involvements of altered immune responses in the mouse kidney. Specifically, the elevation in the expression levels of genes associated with renal inflammation by systematic metabolic abnormalities was reversed by gut colonization of Bacteroid spp. Moreover, gene expression profiles of colon tissues from Bacteroid spp-treated CKD mice showed that genes related to endotoxic shock responses were differentially expressed, highlighting potential organ crosstalk with coordinated metabolic and inflammatory responses after Bacteroid spp treatment.

Conclusions：

These experimental findings implicate Bacteroid spp as a promising live biotherapeutic product for CKD, providing potential avenues for microbiome-based modality of renal insufficiency.

Key words：

Basteroid spp, live biotherapeutic products, metabolomic, microbiome, single-cell sequencing, spatial transcriptome.

B010

Focal adhesion kinase signaling manages functional aquaporins positioning in renal epithelial cells of nephron in mice

黏著斑激酶訊號傳導調度小鼠腎上皮細胞內功能性水通道蛋白的定位

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Background：

Focal adhesion kinase (FAK) is a non-receptor kinase associated with integrin based focal adhesion and converts mechanical stimuli to biochemical signal to renal epithelial cells. It is known active FAK cascades microfilament reorganization in renal epithelial cells to withstand the osmotic pressure stress, even so couple of studies narrated that FAK signaling participated to podocytes foot processes, and renal fibrosis.

Methods：

To clarify pathological or physiological roles of FAK in kidney, the mice undertook FAK inhibitor VS-4718 administration. To obtain data for renal functions in FAK inhibitor treated mice, urine production was monitored, and blood and urine samples were subjected to biochemical analysis. Kidney tissues were subjected to histochemical examinations, immunohistochemical and immunofluorescent staining investigations.

Results：

Daily urine volume increased in the mice with VS-4718 administration. Also, plasma sodium was lowered in the mice who had VS-4718 treatment. Gaining pathological aspect in response to VS-4718, renal tubular injuries were visible of brush border lesion and cell atrophy in the outer stripes and the inner stripe of the outer medulla by periodic schiff staining (PAS). Immunofluorescent staining confimed the colocalization of aquaporin-2 (AQP2) and F-actin which had much pronounced staining at the cell periphery. In the presence of VS-4718, F-actin was more diffusive increased with staining in the cytoplasm, suggestive of F-actin depolymerization. In addition, AQP2 was found less colocalized with F-actin.

Conclusions：

The FAK expressed in whole nephron with higher levels in medulla and relatively lower levels in cortex. When its enzymatic activity was abolished, renal tubules in medulla got injured and the positioning of AQP2 altered.

Key words：

Focal adhesion kinase, aquporin

B011

Restoration of Mitophagy in Osteocytes by AST-120 Improves Bone Phenotype in a 5/6 Nephrectomy Mouse Model of Chronic Kidney Disease

AST-120 通過恢復骨細胞粒線體自噬功能改善 5/6 腎切除小鼠模型骨病變

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Objectives: Mitophagy dysfunction is increasingly recognized as a critical factor in the pathophysiology of bone diseases associated with chronic kidney disease (CKD). In this study, we examined the role of mitophagy impairment in osteocytes from a 5/6 nephrectomy (Nx) mouse model, which mimics CKD. Specifically, we investigated whether feeding these mice with AST-120, an oral adsorbent known to reduce circulating uremic toxins, could mitigate the observed mitophagic dysfunction and improve bone health.

Methods: Eight-week-old male C57BL/J6 mice underwent a two-stage 5/6 Nx procedure to induce CKD, while control mice received sham surgeries. Post-surgery, the Nx mice were divided into groups, one receiving a chow diet and another receiving AST-120 supplementation for 10 weeks. Mitophagy dysfunction in osteocytes was assessed via confocal microscopy and seahorse analysis. Serum and urine biochemistry, bone microarchitecture, and osteocyte mitolysosome markers were evaluated.

Results: Our results demonstrated that 5-week Nx mice exhibited a significant impairment in mitophagy with increased mitolysosomes, accompanied by deterioration in bone microstructure. However, Nx mice fed with AST-120 for 10 weeks showed a notable restoration of mitophagic function, resulting in improved bone phenotype compared to untreated Nx mice.

Conclusion: These findings suggest that AST-120 may alleviate CKD-associated bone pathology by restoring osteocyte mitophagy, providing a potential therapeutic approach for CKD-related bone disorders.

Keywords: bone, CKD, mitophagy, nephrectomy, AST-120

B012

Bitter Melon and Chlorella Extract Complexes may Have Effects on Improving Metabolism Syndromes

山苦瓜與螺旋藻萃取複合物可能具改善血糖及脂質代謝症候群之功效

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Background：
Metabolic syndrome is characterized by obesity, high blood pressure, and insulin resistance. PPAR ligands improve insulin sensitivity and may reduce atherosclerosis through various mechanisms. Research shows that bitter melon extract has anti-inflammatory properties and activates PPAR, enhancing glucose uptake and lowering insulin resistance in normal and inflamed C2C12 cells. The inflammatory response produces TNF-α, which is associated with insulin resistance. Bitter melon can decrease iNOS expression, reducing TNF-α-induced inflammation and potentially improving insulin sensitivity. C-Phycocyanin (C-PC), a major component of chlorella, contains proteins that chelate ferrous ions, scavenge DPPH free radicals, and exhibit antioxidant effects. Atherosclerosis primarily results from excessive lipid accumulation in blood vessels and LDL oxidation.
Methods：
The experimental process evaluated peptide content, cytotoxicity, and insulin secretion in pancreatic beta cells (RIN-m5F) and cardiac cells (H9c2). Peptide levels were measured using the o-phthaldialdehyde (OPA) method. Cytotoxicity in RIN-m5F cells was assessed via the MTT assay, and insulin secretion was evaluated after pre-treating cells with STZ before glucose incubation. H9c2 cells underwent similar cytotoxicity assessments, along with ELISA assays for ATF6 and CHOP levels, while Western blot analysis assessed stress-related protein expression.
Results：
In our study, H9C2 cardiac cells and RIN-m5F pancreatic β-cells were damaged using LPS and STZ for 24 hours. Treatments with moderate (50 μg/mL) and high doses (250 μg/mL) of peptide combinations significantly reduced cell damage and improved viability, though after 48 hours, viability fell below 60%. In glucose-stimulated insulin secretion tests post-STZ, only Metformin and the chlorella-bitter melon combination showed notable improvements, enhancing insulin secretion after 90 minutes.While STZ/LPS treatment increased ATF6 and CHOP levels, only CHOP was downregulated by the peptides. Metformin, chlorella, and bitter melon peptides significantly decreased CHOP. Western blot analysis showed that these peptides reduced eIF2α phosphorylation and increased p58IPK levels, effectively downregulating PERK and ATF4 in heart cells.
Conclusions：
This study investigated the effects of chlorella and bitter melon peptides on cell damage and glucose-stimulated insulin secretion. Toxicity tests indicated that all samples below 1 mg/mL maintained about 80% cell viability after 24 and 48 hours. Both peptides improved survival in STZ- and LPS-damaged cells and enhanced insulin secretion from pancreatic β-cells. However, combinations of bitter melon peptides were less effective than the individual peptides, likely due to competitive interactions at lower concentrations. Importantly, both chlorella and bitter melon peptides downregulated CHOP, P-EIF2A, PERK, and ATF4 while upregulating p58IPK. These findings may aid in future treatment strategies
Key words：Metabolic syndrome, Insulin resistance, Bitter melon, Chlorella, ATF6, CHOP

B013

Single-cell RNAseq analysis reveals immune landscape in Peritoneal Dialysis Fluid

單細胞 RNA 測序分析揭示腹膜透析液中的免疫圖譜

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Background:

Peritoneal dialysis (PD) is a common renal replacement therapy extensively used for individuals diagnosed with end-stage renal diseases (ESRD). However, the roles of different cell populations in peritoneal fibrosis associated with dialysis remain poorly understood.

Methods:

Single-cell transcriptomics from effluent of patients with Early peritoneal dialysis (below 1-2 years, n=5), Intermediate peritoneal dialysis (between 3-6 years, n=5), and Late peritoneal dialysis (above 7-12 years, n=3) were analyzed. Single cell RNA sequencing was performed with Chromium single cell 3' Reagent Kits v3.1 (10X Genomics) according to the manufacturer's protocol. Sequencing data were analyzed by using Cell Ranger and used Seurat package (version 4.0.3) in R program for further analysis.

Results:

A total of 102,698 qualified cells were used in this study. We used UMAP to visualize 28 clusters, and cell type annotation was performed based on the differential expression genes (DEGs) profile of each cluster. We have defined 28 clusters into 7 different cell types, which included NKT cells, Myeloid cells, Mesothelial cells, B cells, pDCs, cDC1s and Neutrophils. NKT cells and Myeloid cells were dominated at all stage of peritoneal dialysis. Compared with the Early PD group, the proportion of Myeloid cells was significantly decreased, while the proportion of NKT cells were significantly increased in Intermediate and Late PD groups. Gradually growing enrichment of inflammation respond pathways were found from short-term dialysis to long-term dialysis, respectively. Furthermore, the intercellular crosstalk based on ligand- receptor interactions were also performed to highlight the possible intercellular communication between each cell type during PD.

Conclusions:

By assessing functional differences of cell types at single-cell resolution, we discovered different cell types that correlated with distinct functions in PD. This research provides deeper understanding of PD biology, which can be valuable for improving the diagnosis and treatment of PD.

Key words:

Peritoneal dialysis, scRNA-seq, Fibrosis

B014

Two new histone deacetylase inhibitors for bladder cancer therapy

兩種具膀胱癌療效的新型組蛋白去乙醯酶抑制劑

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Background: According to the Globocan 2020 report of WHO Global Cancer Observation, bladder cancer is the 10th in terms of incidence and 13th in terms of mortality among all types of cancer worldwide. Bladder cancer has a high recurrence rate, which indicates that the therapeutic effects of advanced bladder cancers are still limited. Vorinostat, a histone deacetylase inhibitor for class I and II of histone deacetylases (HDAC), has been applied to treat cutaneous T-cell lymphoma. In this study, we designed vorinostat-cyproheptadine derivate compound A (8C) and compound B (O8C) for bladder cancer treatment.

Results: 8C and O8C have an IC_{50} of 4.5 μM and 4 μM in 5637 cells, 8 μM and 9 μM in BFTC 905 cells, respectively. In *in vitro* assays, vorinostat, 8C and O8C treatment slightly increased ROS level, decreased mitochondria membrane potential (MMP), and induced apoptosis following the increased percentage of cell cycle in sub-G1 phase for 5637 cells, while a cell cycle arrest was found in G0/G1 phase for BFTC 905 cells. Apoptosis is slightly seen in both cells by the assay of Annexin V-PI dual staining assay, which is associated with a minor rescued cell viability after Z-VAD-FMK pretreatment. Furthermore, among the treated ROS scavengers (*N*-acetyl-*L*-cysteine, setanaxib, and mitoquinone mesylate), only *N*-acetyl-*L*-cysteine shows a minor viability rescue, indicating ROS may not play an important role in 8C- and O8C-induced cell death. In terms of HDAC activity inhibition, vorinostat, 8C, and O8C all exhibited increased expression of H3K9ac and H3K27ac, and decreased HDAC activity, indicating that 8C and O8C have HDACi properties similar to those of vorinostat. In *in vivo* assay, mice underwent intraperitoneal injection treatment of 8C, resulting in delaying tumor growth compared to the treatment of cyproheptadine, vorinostat or O8C individually. Notably, 8C was shown to be the most effective compound for tumor inhibition *in vivo* among all the chemicals. Because the water solubility of 8C is not good, therefore we use its salt form 8C-HCl for further study. In *in vivo* assay, mice underwent gavage treatment of 8C-HCl, also resulted in delaying tumor growth.

Conclusions: Based on the synergistic effect of the combination of vorinostat and cyproheptadine, in this study, we demonstrated that the vorinostat-cyproheptadine derivate compounds enhanced tumor suppressive effect in *in vitro* assay. In *in vivo* analysis, the new compounds 8C and 8C-HCl exhibit a better anti-tumor effect compared with cyproheptadine and vorinostat individually in a homograft ectopic mice model (MB49-C57BL/6).

Key words: bladder cancer, vorinostat, cyproheptadine, HDAC inhibition

B015

Indoxyl sulfate is associated with cognitive impairment in ESRD patients by activating the extrinsic apoptosis in the neuronal cells during differentiating process.

硫酸吲哚酚藉由活化分化中神經細胞之外源性凋亡造成末期腎病病患認知障礙的相關性研究

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Background：

This study investigates the correlation between indoxyl sulfate (IS) levels and cognitive impairment in end-stage renal disease (ESRD) patients from human study, in vivo and in vitro study.

Methods：

In human study, IS concentration was compared between a control group (n=17), an ESRD group with (n=14) and without cognitive impairment (n=17) cognitive impairment. A CKD animal model induced renal impairment in adenine-fed C57BL/6 mice was assessed with behavioral changes by 8-arm maze and new object recognition test. The activity of choline acetyltransferase activity and GFAP were evaluated by immunohistochemical stain in hippocampus. Differentiating SH-SY5Y cells were treated with IS, assessing cell viability and apoptosis flow cytometry and western blotting. Reactive oxidized species generation was measured using DCFCA fluorescence.

Results：

In ESRD patients with cognitive impairment, IS levels were significantly higher compared to healthy controls along with decrease of white matter fiber by fixel-based analysis. CKD mice exhibited renal impairment and memory loss, accompanied by altered choline acetyltransferase and GFAP expression. IS treatment induced early apoptosis in SH-SY5Y cells, associated with increased cleaved caspase 3 levels and Fas/Fas-ligand activity, altered Bax/Bcl2 ratio, and reactive oxidized species generation

Conclusions：

Elevated IS levels are associated with cognitive impairment and neuronal apoptosis, potentially mediated by oxidative stress. IS could be a therapeutic target for cognitive dysfunction in CKD

Key words：

Cognitive impairment, End stage renal disease, indoxyl sulfate, extrinsic apoptosis, choline acetyltransferase, memory loss

B016

The Essential Role of O-Antigen in Uropathogenic E. coli-Induced Neutrophil Extracellular Trap Formation

O 抗原在泌尿道致病性大腸桿菌誘導的嗜中性細胞胞外誘捕網形成中的重要作用

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Background: Urinary tract infections (UTIs) are one of the most common bacterial infections, with uropathogenic *Escherichia coli* (UPEC) being the leading cause. The lipopolysaccharides (LPS) on UPEC's outer membrane are critical in modulating the host immune response. Neutrophil extracellular traps (NETs) are an innate defense mechanism against bacterial infections, but the precise role of LPS in NET formation remains unclear. This study aims to elucidate the mechanism by which UPEC LPS triggers NET formation and to identify the LPS domains that play a key role in modulating NET-mediated bacterial killing.

Methods: We generated UPEC CFT073 mutants by deleting specific LPS biosynthesis genes, including *rfaD* (inner core synthase), *rfaL* (O-antigen ligase), and *wzzE* (O-antigen polymerase). These mutants were used to evaluate NETs formation, reactive oxygen species (ROS) production, IL-1β secretion, and activation of the TLR4/JNK signaling pathway in neutrophils.

Results: Our findings reveal that the O-antigen of UPEC CFT073 LPS is essential for inducing NET formation via the TLR4/JNK/NOX pathways. Inhibition of these pathways significantly reduced ROS production, NETs formation, and IL-1β secretion, underscoring the pivotal role of the O-antigen in this immune response.

Conclusion: This study demonstrates that the O-antigen of UPEC LPS plays a critical role in ROS-dependent NET formation and IL-1β secretion. These findings highlight the importance of the O-antigen in neutrophil-mediated defense against UPEC, suggesting its potential as a therapeutic target for UTIs.

Keywords: Uropathogenic *Escherichia coli* (UPEC), Lipopolysaccharide (LPS), Neutrophil Extracellular Traps (NETs), O-antigen

B017

Effects of SGLT2 inhibitors on modulating protein-bound uremic toxins and gut microbiota in pre-dialysis chronic kidney disease patients: a matched case-control study

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Background and hypothesis: The intricate interplay between chronic kidney disease (CKD) and intestinal microbiota has gained increasing attention, with gut dysbiosis being implicated in uremic toxin accumulation and CKD progression. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are now transforming CKD management but pose uncertain effects on shaping gut microbiota. This study aimed to elucidate the impact of SGLT2 inhibitors on perturbations of gut microbial composition and metabolic responses in CKD patients.

Methods: Analysis of fecal microbiota and targeted profiling of serum short-chain fatty acids (SCFAs) and gut-derived uremic toxins were conducted in 60 CKD patients (treated: n=30; untreated: n=30) and 30 non-CKD controls.

Results: Gut microbial composition differed significantly among three study groups. CKD patients receiving SGLT2 inhibitors exhibited distinctive taxonomic profiles, such as enrichment of *Bacteroides stercoris* and *Bacteroides coprocola.* Surveys of metabolomic profiles revealed a reduction of two uremic solutes, indoxyl sulfate (IS) and p-cresyl sulfate (pCS), and several SCFAs (formic, acetic, propionic, valeric, and 2-methylbutanoic acid) in SGLT2 inhibitor-treated CKD patients. Co-occurrence analysis demonstrated a set of intestinal microbes that is positively or negatively correlated with the levels of pCS, and the abundance of these pCS-associated intestinal microorganisms was correlated with the levels of IS and isovaleric acids in the same and opposite direction, respectively. Further functional prediction indicated attenuated pathways related to protein and carbohydrate metabolism.

Conclusions: Treatment with SGLT2 inhibitors in CKD patients is associated with distinct gut microbial composition and metabolite profiles, suggesting potential modulation of gut dysbiosis and metabolic pathways. Further studies are warranted to elucidate the clinical implications of these findings in CKD management.

Keywords: chronic kidney disease; gut microbiota; sodium-glucose cotransporter 2 inhibitors; uremic toxins; short-chain fatty acid

B018

Long-term proteomic changes from human urinary extracellular vesicles in diabetic patients after administrating SGLT2 inhibitors

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Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors exert their effect by selectively blocking the SGLT2 transporter in the renal proximal tubules and provide nephroprotective effects. However, the long-term effects of SGLT2 inhibitors on human renal proteins and transporters remain unclear.

Method: We collected urine from eighteen patients with type 2 diabetes treated with SGLT2 inhibitors before SGLT2 inhibitors and at 3, 6, 9 months after SGLT2 inhibitors. Urinary extracellular vesicles (uEVs) were isolated by ultracentrifuge. We carried out large-scale LC-MS/MS-based quantitative proteomics from purified uEVs labeled by tandem mass tags.

Results: Characterization of uEVs was confirmed by nanoparticle tracking analysis, transmission electron microscopy, and immunoblotting. Totally, 1108 quantifiable proteins were identified from uEVs. Functional enrichment analysis from upregulated proteins involved in “inhibition of epithelial cell proliferation” and “cell adhesion remodeling”. Downregulated proteins mainly affected cell membrane such as PODXL, ATP1B1, and AQP1. In addition, we identified the co-expressed differentially expressed proteins (DEPs) including upregulated proteins (GPR110, CHMPA4, APPL2, TPPP3) and downregulated proteins (IGHG1, PODXL, SLC4A4, COBLL1) at different time points. After clustering of DEPs from uEVs based on nephron segments, SGLT2 inhibitors recovered the changed renal tubular proteins identified in diabetic patients compared to healthy controls. Among renal solute carrier groups (SLCs), SGLT2 inhibitors mainly affected the SLCs in proximal tubules (SLC5A1, SLC5A2, and SLC4A4) but not the distal tubules (SLC12A1 and SLC12A3). Moreover, proteomic analysis of uEVs in db/db mice administered with SGLT2 inhibitors also showed the changed proteins in terms of “Focal adhesion” and “Slit diaphragm”.

Conclusion: SGLT2 inhibitors affected renal proteins involving changes of membrane proteins and cellular differentiation in diabetic patients. The effects of SGLT2 inhibitors on solute carrier group (SLCs) mainly focused on proximal tubules. This uEVs proteomic study could help us know how long-term effects of SGLT2 inhibitors on human kidney.