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Basic	B001 – B025
Clinical	C001 – C241

基礎研究組壁報發表 Basic Poster

【Basic】

B001-B025 *Chair(s)：陳金順/ Jin-Shuen Chen、洪思群/ Szu-Chun Hung*

B001 The 5-MTP administration alleviate kidney injury in ischemia-induced acute kidney injury in mice

5-MTP 治療在缺血性急性腎損傷的老鼠模型中可減輕腎臟傷害

I-Ching Kuo[1,2], Yen-Yi Zhen[1], Chi-Chih Hung[1], Hung-Chun Chen[1]

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B002 Renal protective effect of Umbelliferone on Acute Kidney Injury in rats via alteration of PI3K/Akt/Nrf2 Signaling Pathway

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B003 Saussurea Involucrata Reduces Renal Injury Caused by Calcium Oxalate Monohydrate.

雪蓮降低單水草酸鈣造成的腎損傷

Yin-Pei Chen[1,3], Yen-Chin Lu[1,3], Jun-Ting Lin[1,3], Hsing-I Tseng[1,3], Li-Fen Huang[5], Yi-Shiou Tseng[1,2,4]

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B004 Albumin overload induces epithelial-mesenchymal transition of podocyte through endoplasmic reticulum stress

白蛋白藉由內質網壓力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]

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B005 SGLT2 inhibitors ameliorate diabetic nephropathy by inhibiting GCLM-mediated oxidative stress and subsequent ferroptosis in proximal tubules
SGLT2 抑制劑透過抑制 GCLM 介導的近端腎小管氧化壓力和鐵死亡來改善糖尿病腎病變
Yi-Chun Tsai[1], Jiun-Chi Huang[1], Ping-Shaou Yu[1], Mei-Chuan Kuo[1], Ya-Ling Hsu[2]
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B006 High glucose and advanced glycation end products may induce renal fibrosis via regulation of NR4A1 and FUBP1
高葡萄糖與糖化終產物可能透過調控 NR4A1 和 FUBP1 誘發腎纖維化
Tzu-Hsuan Yeh[1], Wei-Chih Kan[1, 2], Hsiao-Tung Lin[3], Yi-Hsuan Tsai[3], Yun-Ting Huang[1], I-Ning Yang[1], Jui-Yi Chen[1], Chih-Chiang Chien[1], Chia-Chun Wu[1], Ming-Yan Jiang[1], Yu-Chi Kou[1], Jyh-Chang Hwang[1], Hsien-Yi Wang[1], and Jau-Shyang Huang[2]
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B007 To study the role on Klotho-mediated AKT/Nrf2 pathway in protecting Indoxyl sulfate-mediated HK-2 cells damage
Klotho 蛋白所調節 AKT/Nrf2 路徑於保護吲哚酚硫酸鹽造成近曲腎小管細胞受損機轉探討
C-Y Sun[1*], K-L Tsai[2], and Y-T Chang[3]
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B008 Indoxyl Sulfate Diminishes Renal Hydrogen Sulfide production in Chronic Kidney Disease Rats
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B009 Mechanism ofα-Mangostin on Modulating Renal Fibrogenesis through the Erk-Mediated Singaling Pathway
Li-Yuan Kuo[1], Yi-Hsien Hsieh[2,3], Jen-Pi Tsai[1,4,*]
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B010 Mechanism of Anti-Fibrotic Effects of Ellagic Acid by Modulating Epithelial-Mesenchymal Transition

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B011 Protective effects of phillygenin on pyroptosis-induced renal injury and fibrosis in vitro and in vivo.

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B012 Comparison of cardiovascular outcomes of Febuxostat and Allopurinol usage in patients with Diabetes Mellitus and Chronic kidney disease
比較使用黃嘌呤氧化酶抑制劑和別嘌醇在慢性腎臟病和糖尿病病人的臨床結果

Ming Wang, Hsin Hsiang Huang, Yu-Wei Fang, Ming-Hsien Tsai,
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B013 Inflammation Induces Renal Osteogenesis and Calcification through ERK Signaling Pathway
發炎透過 ERK 訊息傳遞途徑促進腎臟細胞成骨化與鈣化

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B14 TNF-α increases calcium oxalate stone formation in rat kidneys by inducing crystal adhesion proteins
TNF-α 透過誘導結晶黏附蛋白來增加大鼠腎臟中草酸鈣結石的形成

Jun-Ting Lin[1,3], Hsing-I Tseng[1,3], Yin-Pei Chen[1,3], Yen-Chin Lu[1,3], Yi-Shiou Tseng[1,2,4]
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B015 Glycated Tamm-Horsfall protein of diabetic kidney disease patients decrease the function on crystal aggregation inhibition
糖尿病腎病變患者的 Tamm-Horsfall 蛋白糖化會降低對晶體聚集抑制的功能

Yen-Chin Lu[1,3], Jun-Ting Lin[1,3], Hsing-I Tseng[1,3], Yin-Pei Chen[1,3], Yi-Shiou Tseng[1,2,4]
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B016 Breast Cancer cells secreted proteins advance in macrophages infiltration and inflammation in kidney of breast cancer mice
乳癌细胞分泌之蛋白質促進乳癌小鼠腎臟之巨噬细胞浸潤和發炎反應
Lu-Heng Lu [1,2,3], Seng-Wen Niu [1,2,3,4], Chi-Chih Hung [1,2,3,5], Hung-Chun Chen [1,2,3,5]
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B017 Salinomycin Attenuates Kidney Fibrosis and Inflammation in Mice with Unilateral Ureteral Obstruction
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B018 S-Nitrosylation of Tissue Transglutaminase in Modulating Glycolysis, Oxidative Stress, and Inflammatory Responses in Normal and Indoxyl-Sulfate-Induced Endothelial Cells
組織轉谷氨酰胺酶的 S-亞硝基化調節正常和硫酸吲哚酚誘導的內皮細胞的糖酵解、氧化壓力和發炎反應
Cheng-Jui Lin [1,2,3], Hong-Mou Shih[1] , Chun Yu Chiu [4] , En-Chih Liao [4] , Chih-Jen Wu [1,2,3], Ching-Hu Chung [2] and Thung-S. Lai [4]
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B019 IXA4, a selective XBP1s inducer, ameliorates AKI to CKD-related renal fibrosis
Wen-I Chen[1], Jia-Huang Chen[1], Tsai-Chen Chiang[1], Shao-Yu Yang[2], Jenq-Wen Huang[2], Chih-Kang Chiang[1,2,3], Kuan-Yu Hung[3]
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宋志建 [1], 張欣儀 [2], 陳敏修 [1], 羅以筑 [1], 許育瑞 [1], 林石化 [1]
Chih-Chien Sung[1], Hsin-Yi Chang[2], Min-Hsiu Chen[1], Yii-Jwu Lo[1], Yu-Juei Hsu[1], Shih-Hua Lin[1]
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B021 Activated state of ESKD patient T cells induced by soluble interleukin-15
介白素 15 誘發末期腎臟病人T細胞之活化狀態
Kai-Hsiang Shu[1,5], I-Yu Chen[1], Hsiu-Jung Liao[2], Yen-Ling Chiu[1,2,3,4]
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B022 Mechanims of Licochalcone A Onf Suppressing Renal Cell Carcinoma By Modulating Sp1-Mediated Lc3 Expression

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B023 Mechanism of Corosolic Acid on Suppress Metastasis Of Human Renal Cancer Cell By Targeting Erk/Mmp-9 Expression

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B024 The anti-cancer effect of two-drug combination regimens in bladder cancer cell lines
抗癌藥物聯合療法在膀胱癌細胞株的藥效分析

Shou-Chieh Wang[1], Yi-Wen Liu[2], Jin-Yi Wu[2], Hsin-Ting Liu[2]
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B025 Molecular characterization of colistin-nonsusceptible Klebsiella pneumoniae isolates in a tertiary teaching hospital
粘菌素不敏感性肺炎克雷白氏菌分離株的分子特徵:南臺灣醫學中心的世代追蹤性研究

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B001

The 5-MTP administration alleviate kidney injury in ischemia-induced acute kidney injury in mice

5-MTP 治療在缺血性急性腎損傷的老鼠模型中可減輕腎臟傷害

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Background：

Hypotension is a risk factor associated with acute kidney injury (AKI) development, and subsequent glucose deprivation and hypoxia in renal epithelial cells might occur. Cilium, a microtubule-based organelle extends from apical of renal epithelial cells and protrudes to tubular lumen, is widely regarded as mechanical sensor of urine flow. Liver kinase B1 (LKB1) in cilia mediates a variety of chemokine signaling including cilium dynamics in renal epithelial cells. Deficiency of LKB1 cascades pathological development of renal fibrosis.

Methods：

As 5-MTP (5-methyltryptophan) is able to activate LKB1 in renal cells, we proposed to investigate the pharmacological effect of 5-MTP on mitigating pathological progression in the ischemia-induced AKI model. Additionally, glucose deprivation and hypoxia as an equivalent etiological scenario of AKI was settled to study LKB1 signaling in renal epithelial cells, and ciliary disorders were also investigated.

Results：

We identified that hypoxia or glucose deprivation in ischemic kidney injury resulted in absence of LKB1 expression in cell cortex and reduced acetylated α-tubulin (a constituent of the primary cilium) and CEP55, which is a centrosomal protein involved in microtubules bundling in renal epithelial cells. Immunohistochemical examinations on acetylated α-tubulin, CEP55, and activated p-LKB1 in kidney revealed that the active LKB1, acetylated α-tubulin, and CEP55 decreased in the AKI mice. After administration with 5-MTP, cilia in renal tubules were recovered, and CEP55 and acetylated α-tubulin levels in renal epithelial cells were restored in the AKI mice.

Conclusions：

In conclusion, 5-MTP treatment attenuated ciliary dysfunction via activation of LKB1 in AKI mice model.

Key words：

5-MTP, ischmia-induced acute kidney injury, LKB1

B002

Renal protective effect of Umbelliferone on Acute Kidney Injury in rats via alteration of PI3K/Akt/Nrf2 Signaling Pathway

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Background：

Acute kidney injury (AKI) is a serious clinical condition that confers a risk of chronic kidney disease development and a high risk of death. Conversion of acute kidney injury (AKI) into chronic kidney injury (ACI) is linked with a high risk of death. In this study, we aim to examine the effect of Umbelliferone on renal injury caused by ischemia/reperfusion in animal models and investigate its underlying mechanism.

Methods：

Swiss albino Wistar rats were used in this experimental study and rats were divided into 5 groups and acute kidney injury was induced via induction of ischemia/reperfusion in the rats. The left renal tissue was harvested 30 minutes after the start of the experiment to assess the damage caused by ischemia/reperfusion. The morphology of the renal tissue and the levels of various parameters in the serum were evaluated. Additionally, the expression of Nrf2, phosphorylated PKC, AkT, HO-1, and caspase-3 in the renal tissue was determined.

Results：

Umbelliferone remarkably suppressed the level of total protein, creatinine, blood urea nitrogen, bilirubin and albumin. Umbelliferone significantly altered the level of antioxidant parameters like malonaldehyde, catalase, superoxide dismutase, glutathione, glutathione peroxidase and superoxide dismutase. Umbelliferone significantly ($P<0.001$) suppressed the level of inflammatory cytokines like TNF-α, IL-6, IL-1β; inflammatory parameters such as COX-2, PGE2, TGF-β, respectively. Umbelliferone significantly ($P<0.001$) suppressed the expression of p-Akt, Nrf2, HO-1, and pro-caspase-3 and enhanced the expression of caspase-3 in the renal tissue.

Conclusions：

It can be concluded that Umbelliferone protects against renal injury in rats via alteration of PI3K/Akt/Nrf2 signaling pathway.

Key words：

Acute Kidney Disease, Umbelliferone, Inflammation, PI3K/Akt/Nrf2 Signaling pathway

B003

Saussurea Involucrata Reduces Renal Injury Caused by Calcium Oxalate Monohydrate.

雪蓮降低單水草酸鈣造成的腎損傷

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Background：

腎臟中結晶的累積以及黏附會導致腎小管阻塞直接及間接造成腎損傷。結晶性腎病變與急性腎損傷和慢性腎病變有關。雪蓮 (Saussurea involucrata) 是一種高山草本植物，已被證實其所含的生物活性成分能抗發炎、抗氧化、抗腫瘤並具有神經保護作用的藥用價值。當腎臟中結晶的累積及黏附長期影響下會導致腎臟發炎進而造成腎損傷。我們的研究發現雪蓮細胞萃取物 (SE) 可以提高單水草酸鈣 (Calcium oxalate monohydrate，COM) 刺激後 HK-2 細胞 (Human renal cortex proximal tubule cell) 的存活率以及促進傷口癒合的能力，並降低 COM 所誘導的細胞凋亡。

Methods：

MTT 分析測定，觀察 HK-2 細胞在 COM 刺激下以及 COM 合併雪蓮治療後的細胞活性。傷口癒合實驗，使用微量吸管尖端去除培養皿中間部分的細胞，加入雪蓮細胞萃取物 處理 24 小時，觀察 HK-2 細胞的傷口癒合能力。HK-2 細胞以 COM 刺激 24 小時，再加入雪蓮細胞萃取物治療 24 小時，收集全細胞蛋白進行細胞凋亡相關蛋白分析。

Results：

MTT 測定結果顯示，COM 降低了細胞活力，雪蓮萃取物則維持細胞活力。雪蓮萃取物可以提高 COM 刺激下 HK-2 細胞的存活率。在傷口癒合實驗中，雪蓮萃取物促進 HK-2 細胞的傷口癒合能力，雪蓮細胞萃取物增加 HK-2 細胞的傷口癒合面積。雪蓮萃取物提高了用 COM 處理的 HK-2 細胞的存活率、傷口癒合能力並且減少細胞凋亡。

Conclusions：

雪蓮萃取物可以增加細胞存活率、傷口癒合能力並降低 COM 所造成的細胞凋亡。未來將進一步研究其中詳細機轉，希望透過雪蓮細胞萃取物降低 COM 所造成細胞傷害，可做為治療腎損傷的潛力因子。

Key words：

雪蓮、腎損傷、結晶性腎病變、急性腎損傷、慢性腎病變

B004

Albumin overload induces epithelial-mesenchymal transition of podocyte through endoplasmic reticulum stress

白蛋白藉由內質網壓力來引發腎絲球足細胞的上皮間葉轉換

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Background: Proteinuria, predominantly as albuminuria lies in its association with progressive loss of kidney function. Epithelial-mesenchymal transition (EMT) plays a significant role in kidney fibrosis. Podocyte may undergo EMT after injury, leading to podocyte dysfunction that ultimately leads to defective glomerular filtration. The endoplasmic reticulum (ER) plays a major role in post-translational processes including protein folding and the production of functional proteins. The pathophysiology linking albuminuria to loss of kidney function is complex and still incompletely understood. Albuminuria is a both a hallmark and a risk for progressive glomerular disease, and results in increased exposure of podocytes to serum albumin with its factors. The study examines whether albumin overload up-regulates ER stress that induces podocyte undergoing EMT that may increase albumin filtration.

Methods: Podocytes were exposed to medium alone or in high concentrations of delipidated, endotoxin-free human serum albumin (HSA, 10 mg/ml). 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) was measured by real-time PCR and Western blotting.

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

Conclusion: Albumin induced EMT of podocyte through ER stress that may lead to podocyte dysfunction, and the severity of albuminuria and glomerulosclerosis.

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

B005

SGLT2 inhibitors ameliorate diabetic nephropathy by inhibiting GCLM-mediated oxidative stress and subsequent ferroptosis in proximal tubules

SGLT2 抑制劑透過抑制 GCLM 介導的近端腎小管氧化壓力和鐵死亡來改善糖尿病腎病變

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Background：

Diabetes is an increasing threat to human health and diabetic nephropathy (DN) is the leading cause of end-stage kidney disease. Ferroptosis, a form of iron-dependent and non-apoptotic regulated cell death, contributes to kidney injury; however, whether ferroptosis involved in proximal tubular (PT) injury during DN progression and its exact molecular mechanism is poorly understood. In addition, the effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on ferroptosis-mediated DN has not been well-explored.

Methods：

This study used in-vivo and in-vitro models to explore the role of oxidative stress and ferroptosis, and their signaling pathways in PT of DN was determined by bulk RNA sequencing. Reactive oxygen species (ROS) and glutathione were examined. Hoechst 33342 and propidium iodide staining were used to detect ferroptosis. The features of ferroptosis were examined by assessing iron change, lipid hyperoxidation, mitochondrial membrane potential reduction, and glutathione hydroperoxidase 4 expression. Dapagliflozin, one of SGLT2i, was administered to evaluate its therapeutic efficiency in ferroptosis-induced DN

Results：

Our study revealed that high glucose (HG) induced ferroptosis by increasing iron loading, ROS production, and lipid hyperoxidation, and reducing glutathione in PT cells. Transcriptome analysis of primary PT cell obtained from the diabetic patient revealed that glutathione cysteine ligase modifier subunit (GCLM) was involved in regulation of ferroptosis. Suppressing GCLM promoted ferroptosis and overexpression GCLM ameliorated HG-induced ferroptosis in PT. Antioxidants suppressed oxidative stress and ferroptosis in PT of in-vitro and in-vivo models of DN. Furthermore, SGLT2i attenuated ferroptosis of PT in both in vitro and in vivo models, and further rescue PT injury of DN by increasing GCLM expression.

Conclusions：

HG leads to oxidative stress and consequent ferroptosis through GCLM loss in PT. SGLT2i treatment suppresses ferroptosis in PT by enhancing GCLM expression, further ameliorating DN progression. Our study provides a novel molecular mechanism of SGLT2i in DN treatment.

Key words：

sodium–glucose cotransporter 2 inhibitor, proximal tubule, ferroptosis, GCLM, diabetic nephropathy

B006

High glucose and advanced glycation end products may induce renal fibrosis via regulation of NR4A1 and FUBP1

高葡萄糖與糖化終產物可能透過調控 NR4A1 和 FUBP1 誘發腎纖維化

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Background: Reactive oxygen species (ROS) are induced in renal cells in response to high glucose (HG) and advanced glycation end products (AGE). Oxidative stress activates signal transduction cascade and transcription factors, leading to upregulation of genes and proteins involved in the progression of renal fibrosis. Recent evidences demonstrate that the nuclear hormone receptor (NR) superfamily and far upstream element binding protein 1 (FUBP1) may play central roles in the modulation of cellular ROS. Thus, the goal of this study is to investigate the roles of the NR4A subfamily and FUBP1 in the molecular mechanisms regulating renal fibrosis in streptozotocin (STZ)-diabetic mice and HG/ AGE-cultured renal cell lines.

Methods: Protein expression was measured by Western blotting. Cellular hypertrophic growth was evaluated by hypertrophy index. The FUBP1 protein-DNA binding activity was assayed by electrophoretic mobility shift assay.

Results: Our results showed that STZ-induced diabetic mice had obviously decreased NR4A1 protein levels but increased Skp2 phosphorylation in glomerular cells than normal mice for 42 days. Probucol (1.5 mg/kg/day) administration also significantly reversed these effects. On the other hand, FUBP1 protein levels were profoundly affected by HG or AGE treatments in HK-2 cells. Besisdes, we also found that HG/TGF-β1 reduced FUBP1-binding activity in NRK-49F cells.

Conclusion: We found that STZ-induced diabetic mice had obviously decreased NR4A1 protein levels but increased Skp2 phosphorylation in glomerular cells. The antioxidant probucol administration significantly reversed decreased NR4A1 protein level in diabetic renal cortex. NR4A1 and FUBP1 may be involved in the modulating HG/AGE-induced renal fibrosis.

Key words: high glucose (HG); advanced glycation end products (AGE); renal fibrosis; Nuclear hormone receptor (NR) superfamily; far upstream element binding protein 1 (FUBP1)

關鍵字: 高葡萄糖、糖化終產物、腎纖維化、NR4A1、FUBP1

B007

To study the role on Klotho-mediated AKT/Nrf2 pathway in protecting Indoxyl sulfate-mediated HK-2 cells damage

Klotho 蛋白所調節 AKT/Nrf2 路徑於保護吲哚酚硫酸鹽造成近曲腎小管細胞受損機轉探討

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Background：
Chronic kidney disease (CKD) is a prevalent and progressive condition worldwide. The uremic toxin, indoxyl sulfate (IS), is known to have detrimental effects on various organs, including the kidney. Previous studies have shown that IS reduces the expression of the anti-aging klotho protein in proximal tubule cells and kidneys, but the precise mechanism underlying its role in nephropathy remains unclear. In this study, we aim to demonstrate that the downregulation of Klotho following IS stimulation contributes to reduced cell viability and increased cytotoxicity in HK-2 cells (a proximal tubular cell line).
Methods：
The primary renal proximal tubule epithelial cells, HK-2 cells, was obtained. Cell viability was evaluated using the MTT assay. At the end of IS stimulation, cells were washed and the ROS levels were measured by using a fluorescence microplate reader. The Nrf2 activity assay, Mitochondrial complex III activity assay, SOD activity were examined by commercial kit, in addition to Caspase 3 assay. The mitochondrial membrane potential was evaluated using the JC-1 fluorescence dye. One-way analysis of variance (ANOVA) analysis was performed to test differences among groups.
Results：
We will investigate whether recombinant Klotho can reverse the AKT/Nrf2 axis in IS-treated HK-2 cells, leading to the restoration of antioxidant enzymes HO-1, NQO1, and SOD, and a reduction in ROS production. Additionally, we will examine how IS affects mitochondrial function, including changes in mitochondrial membrane potential, mitochondrial COX-III mRNA expression, and mitochondrial complex III activity, and whether these alterations are mediated by the klotho/AKT/Nrf2 axis. Furthermore, our study will explore the involvement of klotho in IS-induced apoptosis of HK-2 cells by examining the expression of Bax, Bcl-2, and cytochrome c using Western blot and caspase-3-positive cells using flow cytometry.
Conclusions：
Our cell-line-based study in IS-stimulated HK-2 cells may reveal the mechanism underlying downregulation of klotho and decreased cell viability, through impaired antioxidant capacity and ROS accumulation, subsequently leading to mitochondrial respiratory chain dysfunction, ultimately apoptosis, and possibly involving inhibition of the AKT/Nrf2 axis. These findings are believed to have significant implications for understanding the pathophysiology in aging CKD process and may offer potential targets for therapeutic interventions.
Key words：
Chronic kidney disease; indoxyl sulfate; Klotho; apoptosis; oxidative stress

B008

Indoxyl Sulfate Diminishes Renal Hydrogen Sulfide production in Chronic Kidney Disease Rats

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Background:

In patients with chronic kidney disease (CKD), plasma hydrogen sulfide (H2S) levels are reduced, which is associated with the deterioration of renal function and progression to end-stage renal disease (ESRD). The decline in H2S levels after dialysis suggests that uremic toxins adversely affect H2S production. However, the precise mechanism by which indoxyl sulfate (IS) impairs H2S production in CKD remains unclear.

Methods:

We induced CKD in male Wistar rats through a 5/6 nephrectomy procedure. After four weeks, the rats were divided into groups and treated with an aryl hydrocarbon receptor (AhR) antagonist known as CH-223191. At the end of the treatment period, we collected urine and obtained blood and kidney tissue samples.

Results:

Nephrectomy in rats resulted in impaired kidney function, tubular injury, hypertension, and reduced renal blood flow. However, administration of the AhR blocker CH-223191 to nephrectomy rats prevented the detrimental effects of IS on the kidneys. Following nephrectomy, renal H2S generation decreased, but CH-223191 restored H2S levels and reduced IS accumulation. Nephrectomy also affected the expression of H2S-producing enzymes and the upstream transcription factor Sp1, which were reversed by CH-223191. Additionally, CH-223191 reduced oxidative stress and lipid peroxidation (malondialdehyde) in nephrectomy rats.

Conclusions:

These findings suggest that CH-223191 protects against kidney damage by mitigating the effects of IS, preserving H2S generation, and reducing oxidative stress in nephrectomy-induced kidney injury. In summary, impaired H2S generation caused by IS renders the kidney vulnerable to oxidative stress damage, representing one of the mechanisms underlying IS-mediated kidney function decline.

B009

MECHANISM OF α-MANGOSTIN ON MODULATING RENAL FIBROGENESIS THROUGH THE ERK-MEDIATED SINGALING PATHWAY

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Objective: α-Mangotin (α-MG), a natural derivative of coumarin, was well known as having anti-inflammatory, antioxidant and anti-fibrotic effects of multiple diseases, but its role in mediating the process of renal fibrosis remained unknown

Methods and Results This study used an in vivo unilateral ureteral obstruction (UUO) model and in vitro with HK2 cell lines treated with α-MG and transforming growth factor β1 (TGF-β1). In vitro, α-MG was shown to decrease the ability of motility as well as decreased expression of epithelial-mesenchymal transition (EMT) related factors, including elevated expression of α-SMA, vimentin, collagen-I and N-cadherin by western blot analysis as well as qRT-PCR of HK2 cells co-incubated with TGF-β1. α-MG could downregulate ERK phosphorylation and then decrease the expression of TGF-β1/Smad2/Smad3 with the results of decreased expression EMT related proteins. In vivo, there was reduced expression of α-SMA, vimentin, and collagen-I detected by immunohistochemical stain as well as decreased expression of α-SMA, collagen-I, and vimentin by western blot analysis. While co-treatment with AST-120, α-MG could alleviate more the expression of EMT related proteins, including α-SMA, collagen-I, vimentin, Snail, and Slug as well as the scores of fibrogenesis of UUO kidneys.

Conclusion α-MG was shown to inhibit migration of HK2 cells along with suppressing expression of α-SMA, vimentin, N-cadherin, Snail, Slug, Smad2, and Smad3. Additionally, α-MG could inhibit TGF-β1 induced or UUO induced fibrogenesis through the ERK-mediated signaling pathway. These findings improved our understanding of the role of α-MG in inhibiting the process of fibrogenesis of renal tissues induced by UUO mice and TGF-β1, respectively and suggested that α-MG have a beneficial role in the progression of CKD.

B010

Mechanism of Anti-Fibrotic Effects of Ellagic Acid by Modulating Epithelial-Mesenchymal Transition

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Objective: Ellagic acid (EA)), a kind of polyphenol found in numerous fruits and vegetables, was well known as having anti-inflammatory, anti-apoptotic, antioxidant and anti-fibrotic effects against a variety of diseases, but its role in mediating renal fibrogenesis remained unknown.

Materials and methods: C57BL/6 mice were orally administered EA for 7 consecutive days before and after UUO surgery. Immunohistochemical analysis, reverse transcription-polymerase chain reaction (RT-PCR), and western blotting were used to detect the expression levels of EMT markers. In HK-2 cells treated with TGF-β1, EA was shown to decrease the ability of motility as well as decreased expression of α-SMA, collagen-I, fibronectin, N-cadherin and vimentin by western blot analysis. In vitro studies were performed using the TGF-β1-stimulated HK2 cell line by EA treatment.

Results: This study used an in vivo unilateral ureteral obstruction (UUO) model and in vitro with HK-2 cell lines treated with EA and transforming growth factor β1 (TGF-β1). In UUO mice fed with EA, both microscopical examination with immunohistochemical stain and protein analysis by western blot showed less expression of fibrotic- (α-SMA, fibronectin and collagen I) and epithelial-mesenchymal transition (EMT) (vimentin and N-cadherin) related proteins, compared with sham control. In HK-2 cells treated with TGF-β1, EA was shown to decrease the ability of motility as well as decreased expression of α-SMA, collagen-I, fibronectin, N-cadherin and vimentin expression.

Conclusion EA was shown to alleviate the morphological transformation and concomitantly suppress the expression of fibrotic- and EMT-related proteins in vitro and in vivo. These findings improved our understanding of the role of EA in suppressing the process of renal fibrogenesis and indicated the promising role of EA in the progression of CKD.

B011

Protective effects of phillygenin on pyroptosis-induced renal injury and fibrosis *in vitro* and *in vivo.*

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Background: In Taiwan, the prevalence rate of Chronic Kidney Disease (CKD) among adults is as high as 12%. Patients may suffer from multiple diseases and severe cases, which leads to kidney dialysis or even death. Pyroptosis is one type of programmed cell death that causes the rupture of cell membranes and the release of inflammatory cytokines to exacerbate kidney damage. However, the roles of the pyroptosis in the progression of CKD remains unclear. Phillygenin (PHI) is one of the functional ingredients of Forsythia, which has been demonstrated to the anti-inflammatory, anti-fibrotic, and anti-oxidative properties. Therefore, in this study, we aim to investigate whether PHI treatment improves the progression of CKD by regulating pyroptosis *in vivo* and *in vitro*.

Methods: *In vivo,* C57BL/6 mice were administrated with surgical UUO procedure, and then treated with PHI (25 mg/kg) for 14 days. *In vitro,* NRK52E cell lines were pretreated with PHI (20 μ M) for an hour, and co-treated with LPS(10 μ g/ml) and ATP (3 mM) for 0.5, 4, 8, 16 hours.

Results: In the UUO mice, the protein expression levels of fibrotic proteins (such as Fibronectin, Vimentin, and α-SMA), inflammatory factors (such as COX-2, TNF-α), and apoptosis-related proteins (such as Caspase-3 and Bax) were significantly elevated, which was relieved after PI treatment. Similarly, the expression of pyroptosis-related proteins markers including, NLRP3 and GSDMD and the downstream inflammatory markers including Caspase-1, and IL-1β, was also prominently alleviated after administration of PHI. *In vitro,* after combined ATP and LPS treatment, the expression of the pyroptosis-related proteins was significantly elevated at different time points, which could be significantly reversed by PHI treatment in NRK52 cells

Conclusions: Our results suggested that PHI treatment ameliorates renal fibrosis, inflammation, and apoptosis. Furthermore, PHI treatment can also improve pyroptosis signaling through the NLRP3/Caspase-1/GSDMD pathway. PHI could potentially serve as a therapeutic target to alleviate the progression of CKD in the future.

Key words:

chronic renal disease, fibrosis, phillygenin, pyroptosis, unilateral ureteral obstruction

B012

Comparison of cardiovascular outcomes of Febuxostat and Allopurinol usage in patients with Diabetes Mellitus and Chronic kidney disease

比較使用黃嘌呤氧化酶抑制劑和別嘌醇在慢性腎臟病和糖尿病病人的臨床結果

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Background
Hyperuricemia is a biochemical aberration especially in chronic kidney disease (CKD) patient. Febuxostat (Febuxostat) is a promising uric acid lowering agent because of its low allergic reaction. However, the benefit and risk of Febuxostat in early CKD with DM patient are controversial. Some researchers had shown Febuxostat at having high risk of cardiac vascular (CV) death, but others showed opposite conclusion. Thus, we aimed to conduct a study to elucidate the effect of Febuxostat on CV risk compared to the first line urate-lowering agent allopurinol in chronic kidney disease patient.
Methods
Design: A retrospective cohort study
Setting: Taiwan, a National Health Insurance Research (NHIRD)
Participants: Participants are the patient using allopurinol or Febuxostat that had received diagnoses of CKD and Diabetes between 2012 to 2017. To make sure that the patient's renal function was more than 30 ml/min/1.732, all the patients should have metformin prescription concurrently. Patients using Allopurinol were grouped into the case group (n = 12901) and patients using Febuxostat were grouped into the control group (n = 2997). A propensity score matching with a 1:1 ratio was performed and finally a balance patient number was got (n = 2997 in both arms).
Main outcomes: We used the competing risk model to estimate the hazard ratios (HRs) for long-term outcomes including total admission rate, CV intervention admission rate and heart failure admission rate.
Results:
Before propensity score matching and after propensity score matching, the febuxostat users showed a significant increment risk in all cause hospitalization (HR: 1.33, 95% CI 1.24–1.41;P <0.001), hospitalization for heart failure (HR:1.60, 95% CI 1.42–1.81; P <0.001) and hospitalization for CV intervention (HR: 1.52, 95% CI 1.32–1.74; P <0.001) than allopurinol group in all our models. Moreover, the hazardous effect of febuxostat on cardiac health were observed consistently across various subgroups within our study.
Conclusion:
Our investigation suggests that the use of febuxostat may be associated with increased risks for cardiovascular complications in the diabetic patient with mild to moderate CKD. These findings emphasize the need for careful consideration when prescribing febuxostat in this high-risk population. Further randomized controlled trials are needed to confirm our study results in a medical context.
Key words: Febuxostat, allopurinol, cardiovascular events, mortality, hyperuricemia, heart failure

B013

Inflammation Induces Renal Osteogenesis and Calcification through ERK Signaling Pathway

發炎透過 ERK 訊息傳遞途徑促進腎臟細胞成骨化與鈣化

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Background：
結晶性腎病變 (crystal nephropathy) 指尿液中過飽和礦物質之結晶造成腎損傷，進而誘發急性腎損傷、慢性腎臟病或鈣質沉著症等腎臟疾病。過去研究指出慢性腎臟病病人腎臟中參與成骨化的蛋白表現量隨疾病發展而提升，並與發炎反應呈正相關而與腎功能呈負相關。另些研究則發現高鈣尿 (hypercalciuria) 大鼠腎臟的成骨蛋白增加，在人類磷酸鈣結石之腎臟也觀察到成骨蛋白。此外，在其他疾病如血管鈣化中促發炎細胞激素會提升成骨蛋白表現，但同樣的機制在腎臟疾病中則尚未被探討。這些證據暗示著發炎反應可能使腎細胞表現成骨蛋白，促進成骨化及磷酸鈣結晶沉積，長期可能誘導慢性腎臟病的產生，是為本研究的目標。
Methods：
為探討發炎反應是否促進腎臟磷酸鈣沉積，我們給予大鼠 8 周的高鈣飲食並在第 4 周以單側輸尿管結紮手術誘導腎臟發炎，以 Von Kossa 染色及顯微紅外線光譜儀確認大鼠腎臟磷酸鈣的沉積情形，並以免疫組織化學染色法與西方點墨法分析腎臟組織的成骨蛋白。另給予腎小管上皮細胞 HK-2 促發炎細胞激素，探討發炎反應誘導成骨蛋白表現之訊息傳遞途徑。
Results：
透過高鈣飲食搭配發炎反應建立腎臟磷酸鈣沉積的大鼠模型，發現發炎反應會加速高鈣飲食誘導的磷酸鈣沉積，並顯著提升腎臟組織的 OPN 與 Runx2 等成骨蛋白表現。給予 HK-2 細胞高鈣環境或是促發炎細胞激素都能上調 OPN、OPG 與 ALP 等成骨蛋白的表現，再次驗證動物實驗的結果。我們進一步探討促發炎細胞激素是否透過其下游 ERK 訊息傳遞途徑提升成骨蛋白表現，發現給予 ERK 抑制劑能夠降低促發炎細胞激素上調成骨蛋白的效果，顯示促發炎細胞激素的確經由 ERK 訊息傳遞途徑上調成骨蛋白。
Conclusions：
促發炎細胞激素會透過下游 ERK 訊息傳遞途徑上調成骨蛋白，因而加劇了高鈣環境誘導的腎臟細胞成骨化與磷酸鈣沉積，當腎臟長期暴露於磷酸鈣沉積環境下將發生結晶性腎病變，造成慢性腎臟病。我們的研究除了揭示發炎反應誘發腎臟細胞成骨化與鈣化的分子機制外，更建立了簡單且短時程的腎臟磷酸鈣沉積動物模型，以利相關腎臟疾病之研究。

Key words：
結晶性腎病變、磷酸鈣沉積、發炎反應、慢性腎臟病、成骨化

B014

TNF-α increases calcium oxalate stone formation in rat kidneys by inducing crystal adhesion proteins

TNF-α 透過誘導結晶黏附蛋白來增加大鼠腎臟中草酸鈣結石的形成

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Background：

腎臟內晶體引發的炎症反應和細胞壞死過程中會涉及 TNF-α受體（TNFR）的信號傳遞。另外在結晶的滯留與累積上有黏附蛋白參與其中。在腎細胞損傷的情況下，黏附蛋白可以作為晶體粘附到細胞表面的促進劑，將導致結石的形成。有研究證實，高草酸尿液需要 TNFR 參與才能引起 CD44 與 Annexin II 增加晶體黏附形成腎臟草酸鈣結石。因此我們進一步的探討研究，TNF-α是如何調控結晶黏附蛋白的表達，以及 TNF-α抑制劑是否能夠降低草酸鈣結石的形成。希望能在未來提供有效的臨床治療方式。

Methods：

動物實驗中我們給予 Sprague Dawley (SD) rats 腹腔注射 glyoxylate (60 mg/kg/day)連續一週來誘導草酸鈣結石，並同時給予 TNF-α monoclonal antibody (Adalimumab 50 mg/ml)與 TNF-α receptor antagonist (R-7050 12 mg/ml)來當作治療組。細胞實驗中我們用人工合成草酸鈣(COM 10 μg/ml)與人類重組蛋白 TNF-α(25 ng/ml)刺激人類腎臟皮質近端小管細胞(HK-2)，還利用前處理 TNFR siRNA 與 ERK、NF-κB 抑制劑的方式來阻斷 TNF-α訊息路徑。觀察 TNF-α對腎臟細胞的結晶黏附蛋白調控機制，以及對腎臟中草酸鈣結石形成的影響。

Results：

在大鼠實驗中發現，glyoxylate 會誘導腎臟與尿液中草酸鈣結晶的形成，以及增加腎臟中炎症 TNFR1/2 與 Annexin II、OPN 的表現。TNF-α抑制劑能夠明顯減少大鼠尿液與腎臟中的草酸鈣晶體，並且降低腎臟 TNFR1/2 以及 Annexin II、OPN 的表現。另外在細胞實驗中，COM 與 TNF-α都會誘導 HK-2 活化 ERK、NF-κB 以及上調 CD44、Annexin II、OPN 的表達。使用 TNFR siRNA 與 ERK、NF-κB 抑制劑阻斷 TNF-α訊息路徑，可以減少 CD44、Annexin II、OPN 的表現。

Conclusions：

TNF-α會透過 ERK 與 NF-κB 的訊息路徑來上調 Annexin II、OPN、CD44 的生成。因此，抑制 TNF-α訊息路徑可以明顯降低結晶黏附蛋白的表達，間接減少草酸鈣在腎臟中形成結石的風險性。

Key words：

腎結石、草酸鈣、TNF-α、結晶黏附蛋白、ERK、NF-κB。

B015

Glycated Tamm-Horsfall protein of diabetic kidney disease patients decrease the function on crystal aggregation inhibition

糖尿病腎病變患者的Tamm-Horsfall蛋白糖化會降低對晶體聚集抑制的功能

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Background：
Tamm-Horsfall protein (THP) is the most abundant protein in human urine, it plays an important role in preventing kidney stone formation. It has been studied that diabetic kidney disease (DKD) had higher urinary glycated THP, but the function of crystal aggregation inhibition from THP is still unknown. Advanced glycation end products (AGEs) are nonenzymic activities that are formed by proteins, lipids, and amino acids with sugar. Our study aims to investigate the different function of glycated THP on crystal aggregation between stone formers with and without DKD.

Methods：
There were 52 non-DM and 42 DM stone formers included. Salt precipitation method was used to isolate THP from 24-hour urine. Urine THP amount were measured by ELISA to estimate the daily amount, whereas AGEs amount were measured by fluorescent detection. The aggregation test was the interaction between calcium oxalate monohydrate (COM) crystal and THP by a spectrophotometer (optical density at λ620 nm).

Results：
Non-DM stone formers exhibited larger daily urine THP extraction amounts than DM stone formers (13.96 ± 1.14 mg/day vs. 9.77 ± 1.11 mg/day, $P < 0.05$). DM stone formers had considerably lower function of inhibiting aggregation than non-DM stone formers (-3.01 ± 2.00 % vs. 6.53 ± 1.74 %, $P < 0.001$). The high glycated THP group had significantly decreased aggregation inhibition function (DM AGE-THP >500 vs. Non-DM AGE-THP <500, -7.51 ± 3.76 % vs. 9.93 ± 2.27 %, $P < 0.001$). DKD stone formers exhibit higher THP glycation activity levels (DM MDRD <60 vs. Non-DM MDRD >60, 919.48 ± 163.51 AU/mg vs. 488.63 ± 51.26 AU/mg, $P < 0.05$. DM MDRD <60 vs. DM MDRD >60, 919.48 ± 163.51 AU/mg vs. 518.75 ± 78.90 AU/mg, $P < 0.05$). THP from DKD stone formers displayed significantly reduced aggregation inhibition function (DM MDRD <60 vs. Non-DM MDRD >60, -9.60 ± 4.28 % vs. 5.72 ± 2.37 %, DM MDRD <60 vs. Non-DM MDRD <60, -9.60 ± 4.28 % vs. 7.93 ± 2.47 %, DM MDRD <60 vs. DM MDRD >60, -9.60 ± 4.28 % vs. -0.37 ± 2.08 %).

Conclusions：
According to our findings, stone formers with DKD have higher glycated THP levels and impaired THP function on crystal aggregation inhibition.

Key words：
Glycated THP, DKD, renal function, crystal aggregation.

B016

Breast Cancer cells secreted proteins advance in macrophages infiltration and inflammation in kidney of breast cancer mice

乳癌细胞分泌之蛋白質促進乳癌小鼠腎臟之巨噬细胞浸潤和發炎反應

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Background：

The association of nephrotic syndrome with solid tumor is considered as cancer cells released nephrotoxic molecules elicited pathophysiological progression. At present, there are various pathological features, including macrophage infiltration, collapsing focal segmental glomerulosclerosis, and casting nephropathy, observed in clinical presentation of malignancy.

Methods：

Advancing in macrophage-based pathological development in kidney of breast cancer mice, the breast cancer bearing BALB/c mice BALB/c mice were established with orthotopic implantation of 4T1-luc2 cells. Additionally, bone marrow derived monocytes (BM-monocyte) and Breast cancer - secreted protein (BCSeP) stimulated BM-monocytes were introduced to tail vein 7 days post 4T1-luc2 cells implantation in order to validate role of BCSeP acting in macrophage infiltration to and inflammation in kidney. CD11b antibody marked macrophages and gp80 antibody against IL-6 receptor were employed to index macrophage infiltration and inflammation in kidney of breast cancer mice, breast cancer mice with monocytes, and breast cancer with BCSeP stimulated monocytes.

Results：

The immunofluorescent examinations on macrophage, and gp80 expression evidence that few macrophages present and less gp80 expression detected in kidney of breast mice without adding BM-monocytes. It appeared in the breast cancer mice with BM-monocytes or BCSeP educated BM-monocytes displayed massive macrophages distributed in glomeruli, and peritubular spaces. Otherwise, the higher gp80 expression was detected the kidney in the breast cancer mice with BCSeP educated BM-monocytes, compared to lower gp80 detected in kidney of breast cancer mice with/without BM-monocytes. The IL-10 and TGF-b upregulation were quantitated in the macrophages with BCSeP stimulation.

Conclusions：

Taking together, the breast cancer secreted proteins entail pathological factors that are capable of stimulating monocytes differentiated to M2 macrophage. Also, breast cancer secreted proteins remotely induce M2 macrophage infiltration to kidney, and drive microphage-mediated renal inflammation.

Key words：Breast cancer, M2 macrophage infiltration, kidney injury

B017

Salinomycin Attenuates Kidney Fibrosis and Inflammation in Mice with Unilateral Ureteral Obstruction

鹽黴素減輕單側輸尿管阻塞小鼠的腎臟纖維化和炎症

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Background:

Renal fibrosis is a key pathological phenomenon in chronic kidney disease (CKD) leading to the progressive loss of renal function. Salinomycin is an antibiotic isolated from Streptomyces albus that also regulates cell fates, but its role in renal fibrosis is unclear. We examined the effects of salinomycin on renal fibrosis in vivo and on TGF-β1-induced renal fibroblast activation in vitro.

Methods:

A unilateral ureteral obstruction (UUO) model was induced in male B6 mice. Mice with UUO were administered with salinomycin or saline intraperitoneally 1 day before UUO surgery and daily thereafter. Both kidneys were harvested 7 days after surgery for further analysis. For the in vitro experiments, NRK-49F rat fibroblasts were pre-incubated with salinomycin before TGF-β1 stimulation. The inhibitory effects of salinomycin on signaling pathways down-stream of TGF-β1 were analyzed.

Results:

In UUO mice, salinomycin administration ameliorated tubulointerstitial fibrosis as shown by Masson's trichrome staining in accordance with the reduced mRNA and protein expressions of fibronectin, collagen type I/IV, in the UUO kidneys. In addition, inflammasome mRNA expression in the UUO kidney was also suppressed by salinomycin. In vitro, salinomycin treatment inhibited the induction of fibronectin, collagen type I/IV, and α-smooth muscle actin in NRK-49F cells treated with TGF-β1. Furthermore, the inhibitory effects of salinomycin were associated with down-regulation of Smad2/3 and MAPK-p38 phosphorylation.

Conclusions:

Taken together, these findings suggest that the salinomycin may serve as a potential drug to antagonize renal fibrosis in CKD.

Key words:

Salinomycin, Kidney fibrosis, Unilateral ureteral obstruction, TGF-β1

B018

S-Nitrosylation of Tissue Transglutaminase in Modulating Glycolysis, Oxidative Stress, and Inflammatory Responses in Normal and Indoxyl-Sulfate-Induced Endothelial Cells

組織轉谷氨酰胺酶的 S-亞硝基化調節正常和硫酸吲哚酚誘導的內皮細胞的糖酵解、氧化壓力和發炎反應

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Introduction: Circulating uremic toxin indoxyl sulfate (IS), endothelial cell (EC) dysfunction, and decreased nitric oxide (NO) bioavailability are found in chronic kidney disease patients. NO nitrosylates / denitrosylates a specific protein's cysteine residue(s), forming S-nitrosothios (SNOs), and the decreased NO bioavailability could interfere with NO-mediated signaling events.

Method: We were interested in investigating the underlying mechanism(s) of the reduced NO and how it would regulate the S-nitrosylation of tissue transglutaminase (TG2) and its substrates on glycolytic, redox and inflammatory responses in normal and IS-induced EC injury.

Results: TG2, a therapeutic target for fibrosis, has a Ca2+-dependent transamidase (TGase) that is modulated by S-nitrosylation. We found IS increased oxidative stress, reduced NADPH and GSH levels, and uncoupled eNOS to generate NO. Immunoblot analysis demonstrated the upregulation of an angiotensin-converting enzyme (ACE) and significant downregulation of the beneficial ACE2 isoform that could contribute to oxidative stress in IS-induced injury. An in situ TGase assay demonstrated IS-activated TG2/TGase aminylated eNOS, NFkB, IkBα, PKM2, G6PD, GAPDH, and fibronectin (FN), leading to caspases activation. Except for FN, TGase substrates were all differentially S-nitrosylated either with or without IS but were denitrosylated in the presence of a specific, irreversible TG2/TGase inhibitor ZDON, suggesting ZDON-bound TG2 was not effectively transnitrosylating to TG2/TGase substrates.

Conclusion: The data suggest novel roles of TG2 in the aminylation of its substrates and could also potentially function as a Cys-to-Cys S-nitrosylase to exert NO's bioactivity to its substrates and modulate glycolysis, redox, and inflammation in normal and IS-induced EC injury.

Keywords: Transglutaminase, Glycolysis, Oxidative Stress, Indoxyl sulfate

B019

IXA4, a selective XBP1s inducer, ameliorates AKI to CKD-related renal fibrosis

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Background:

Endoplasmic reticulum (ER) stress has been identified as a mediator of kidney progression. Upon ER stress, the unfolded protein responses (UPRs) are activated to maintain ER proteostasis. Among the different pathways of UPRs, inositol-requiring enzyme 1α (IRE1α)-mediated alternative splicing of X-box binding protein (XBP1) promotes adaptive UPRs by enhancing protein folding capacity and ER-associated protein degradation. Our recent work has demonstrated that the down-regulation of XBP1 promotes the transition from AKI to CKD. To translate this concept into clinical application, we applied IXA4, a selective XBP1s activator, in preclinical study.

Methods:

Human kidney proximal tubular epithelial cells (HK2) were treated with TGF-β to simulate the microenvironment of fibrotic kidneys, and IXA4 was co-administered for 24-48 hours. In animal models of unilateral ischemia-reperfusion injury (uIRI) and unilateral ureteral obstruction (UUO), mice received IXA4 treatment through intraperitoneal (ip) injections once daily during the specified time points.

Results:

In vitro experiments using HK2 cells demonstrated that IXA4 treatment had positive effects. It reduced pro-fibrotic processes, epithelial-mesenchymal transition (EMT), pro-inflammation, and G2/M cell cycle arrest induced by TGF-β, a key factor in kidney disease progression. IXA4 was then tested in an AKI to CKD animal model, specifically using unilateral ischemia-reperfusion injury (uIRI). IXA4 significantly decreased connective tissue growth factor (CTGF) protein expression, suggesting a potential reduction in fibrosis. In the case of unilateral ureteral obstruction (UUO), IXA4 treatment slightly ameliorated fibrosis or EMT.

Conclusions: XBP1 splicing promoted by IXA4 alleviated pro-fibrotic processes, EMT, and G2/M cell cycle arrest induced by TGF-β in vitro. Furthermore, when tested in vivo, IXA4 appeared to play a potential role in retarding kidney progression. These findings suggest that further research is required to fully understand the effectiveness of IXA4 in the complex in vivo environment.

Keywords: chronic kidney disease, ER stress, XBP1s, IXA4

B020

RNAseq of Microdissected CCDs Revealing Early Signaling Mediating the Loss of Aquaporin 2 after K^+ Deprivation

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Background: Potassium (K^+) deficiency could cause a reduction in urinary concentrating ability, resulting in nephrogenic diabetes insipidus (NDI), but the detailed mechanism remains unclear. Recently, transcriptomic and proteomic data from acquired NDI models reveal that oxidative stress, apoptosis, and inflammatory signaling are associated with AQP2 loss. We aim to explore the early signaling after K^+ deprivation in collecting ducts.

Method: Immunoblotting were performed at 0, 12, 24, and 48 hours after K^+ deprivation in rats. Serum and urine biochemistry were also recorded. Based on immunoblotting, cortical collecting ducts (CCDs) were microdissected from rats at 6 hrs after K^+ deprivation versus time controls. Single-tubule RNA-Seq was carried out independently in K^+ deprivation rats versus controls (n=4).

Results: Immunoblotting of bulk kidney showed a decreased in AQP2 protein abundance at 12 hours of K^+ deprivation diet, and urine osmolality was significantly decreased at 24 hours, confirming the animal model of K^+ deprivation-induced NDI. Single-tubule RNA-Seq data of CCDs at 6 hrs after K^+ deprivation showed *Aqp2*, *Aqp3*, and *Atp1a1* were significantly downregulated. It also revealed that chemokine transcripts (*Ccl20* and *Ccl28*) were increased significantly. We also carried out analysis of *Gene Ontology Biological Process* terms that are statistically over-represented in the list of 88 "Increased Transcripts" at 6 hrs of K^+ deprivation in CCDs, and many of the terms are related to glutathione metabolic process (*Gstm1*, *Gsta1*, *Gstt3*, *Txnrd3*), positive regulation of ERK1 and ERK2 cascade (Nrp1, *Ccl20*, *Ripk2*, *Fgfr4*, *Fgfr3*), cell chemotaxis (*Ccl20*, *Ccl28*, *Hbegf*), cellular response to lipopolysaccharide (*Ccl20*, *Ripk2*, *Cd14*, *Tfpi*), consistent with an inflammatory response.

Conclusion: Our small samples RNA-Seq from microdissected CCDs in rats showed early cellular signaling changes in activation of oxidative stress and inflammatory signaling causing loss of aquaporin-2 in K^+ deficiency induced NDI

B021

Activated state of ESKD patient T cells induced by soluble interleukin-15
介白素 15 誘發末期腎臟病人T細胞之活化狀態

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Background:
End stage kidney disease (ESKD) patients are manifested by signs of impaired adaptive immunity, including but not limited to elevated infection-related morbidity and mortality, poor vaccination response, and high atherosclerotic cardiovascular disease burden, which is considered a state of chronic inflammation. The role of adaptive immunity, specifically T lymphocytes, contributing to the proinflammatory state was less clear previously.
Methods:
Peripheral blood mononuclear cells (PBMCs) were isolated from hemodialysis patients and healthy donors. Cytomegalovirus (CMV) serostatus was tested. Lymphocytes were labeled by fixable viability dye and stained with fluorescence-labeled antibodies including CD3, CD4, CD8, CD28, and CD57 and analyzed by flow cytometry. For cytokine production "functionality" analysis, PBMCs were subjected to stimulation by soluble pp65 CMV peptide pool in the presence of anti-CD28/anti-CD49d or plate-bound anti-CD3 antibody, along with addition of anti-CD107a, Brefeldin A and monesin. After staining with surface antibodies, treatment with Cytofix-Cytoperm was applied and followed by intracellular cytokine staining of interferon-γ, interleukin-2, and TNF-α. Enzyme-linked immunoassay was utilized for analysis of plasma from ESKD for cytokines of interest. Ex vivo cultures of healthy donor PBMCs with medium supplemented by soluble factors of interest were harvested and analyzed after 48 hours.
Results:
T cells from ESKD patients were characterized by increased expression of differentiation markers, including loss of costimulatory molecule CD28 and upregulation of senescence marker CD57. Upon stimulation, T cells from ESKD produce more cytokines and were enriched for "polyfunctional" multi-cytokine producing T cells, compared with heathy donor. Analysis of soluble factors from ESKD plasma yielded a trend over increased cytokine concentration. With ex vivo culture of healthy PBMCs, we noted the presence of interleukin-15 in the medium produced an activated profile on T cell cytokine production reminiscent of ESKD T cells.
Conclusions:
ESKD T cells are under an activated state, producing more cytokines, and may contribute to the proinflammatory state of dialysis patients, while IL-15 may be the soluble mediator for this functionality change.

Key words:
Immunology, T cells, ESKD, polyfunctionality

B022

Mechanims of Licochalcone A Onf Suppressing Renal Cell Carcinoma By Modulating Sp1-Mediated Lc3 Expression

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Objective: Licochalcone A (LicA) is a strong anti-inflammatory, antioxidant, and anticarcinogenic substance that is useful against a variety of human malignancies. However, its precise mechanism in mediating the development of renal cell carcinoma (RCC) is not entirely understood.

Materials and methods: The cell growth, autophagy and cytotoxicity effect were evaluated with MTT assay, AO staining, LDH assay, colony formation assay and flow cytometry. The anti-metastatic and anti-tumor effect of LicA involved in Sp1 targeting MAP1LC3B (LC3B) expression were evaluated through the in vitro migration/invasion assay, western blotting, siRNA transfection, immunofluorescence staining and ChIP assay. Evaluation of antitumor effect of LicA was using the in vivo xenograft assay.

Results: In this work, LicA was discovered to limit cell growth and survival, induce cell cycle arrest, promote autophagy and LC3B expression, and inhibit the migration and invasion of RCC cells. In addition, the proliferation, migration, and invasion inhibited by LicA were restored by the transfection of siRNA-LC3. The effects of LC3B on the metastatic phenotype of ACHN cells was enhanced with the overexpression of Sp1 or suppressed by inhibiting the phosphorylation of FAK and Src. Finally, LicA showed antitumor properties against RCC in an in vivo xenograft model.

Conclusion Our study demonstrated the chemotherapeutic potential of LicA on proliferation, migration, invasion, and autophagy through the activation of LC3B expression, ultimately modulating FAK/Src signaling pathway-mediated Sp1 expression. These findings illustrate the novel role and molecular mechanisms of LicA against RCC cells.

B023

Mechanism of Corosolic Acid on Suppress Metastasis of Human Renal Cancer Cell By Targeting Erk/Mmp-9 Expression

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Objective: Renal cell carcinoma (RCC) is one of the common malignant tumors in kidney, which has an increasing incidence in Taiwan. Corosolic acid (CA) is a pentacyclic triterpenoid isolated from Lagerstroemia speciosa, which is known to inhibit cancer cell proliferations, metastasis and induce cell death. However, the antimetastasis effect of CA in RCC is still unknown.

Materials and methods: Cell viability were determined using the MTT assay, and the cell cycle phase was assessed by PI staining with flow cytometry. The ability of cell migration/invasion was performed with in vitro migration and invasion assay. Proteinase assay were detected CA targeting protein in RCC cells. The mRNA and protein expression of MMP-9/MMP-2 were measured by western blot and RT-qPCR assay. Clinical significance of MMP-9 in RCC tissues was analyzed from The Cancer Genome Atlas database by using GEPIA and Kaplan-Meier Plotter software. Interaction of CA and MMP-9 were detected by Molecular docking analysis.

Results: We found that CA showed no influence on cell viability, cytotoxicity, cell cycle distribution and apoptosis induction in human RCC cancer cells and normal HK2 cells. CA was revealed to have a significant inhibitory effect on cell migration and invasion through the downregulation of invasion-related MMP-9 expression and p-ERK1/2 activations in RCC cells, indicating that the ERK-MMP-9 axis mediated the CA-inhibited capacity of cellular migration and invasion. Furthermore, molecular docking analysis revealed that CA might bind to MMP-9.

Conclusion This suggests that CA has potential anti-metastatic activity on RCC cells by targeting the ERK/MMP-9 axis.

B024

The anti-cancer effect of two-drug combination regimens in bladder cancer cell lines

抗癌藥物聯合療法在膀胱癌細胞株的藥效分析

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Background：Doxorubicin is a traditional anti-bladder cancer regimen. Vorinostat has mechanism of histone deacetylase inhibition in treating bladder cancer. Cyproheptadine, an anti-serotonin/histamine agent, has been reported to have an anti-cancer effect in vitro and in vivo. We use combination therapy of these marketed drugs for analysis of cell viability in different bladder cancer cell lines 5637 and BFTC 905.

Methods：Bladder cancer cell lines 5637 and BFTC 905 are tested IC50 by individual regimen first. And the combination effect is analyzed using CompuSyn software via various dosage combination assays.

Results：In single drug analysis, the IC50 of doxorubicin, vorinostat and cyproheptadine is 1.8 μM, 0.8 μM, 70 μM in 5637 cells. In BFTC 905 cells, the IC50 of doxorubicin and cyproheptadine is 1.0 μM and 49 μM. The IC50 of vorinostat could not be calculated because the cell viability reaches a plateau of about 50% at 2 μM. In 5637 cells, the 15 dosage combinations of doxorubicin and vorinostat show combination index (CI) values ranging from 0.08 to 1.38. The best CI value is at 0.6 μM doxorubicin and 2.0 μM vorinostat. The 15 dosage combinations of doxorubicin and cyproheptadine show an antagonistic effect because the CI values are all higher than 1. The 15 dosage combinations of vorinostat and cyproheptadine show CI values ranging from 0.615 to 0.955. The best CI value is at 2.0 μM vorinostat and 64 μM cyproheptadine. In BFTC 905 cells, 0.6 μM doxorubicin could significantly enhance the cytotoxic effect of vorinostat at 1, 1.5 and 2 μM. The 15 dosage combinations of doxorubicin and cyproheptadine show CI values ranging from 0.813 to 1.106. In addition, 0.8 μM vorinostat could enhance the cytotoxic effect of cyproheptadine at 24, 30 and 40 μM.

Conclusions：Base on the results of two-drug combination therapy, it suggests that combination of doxorubicin and vorinostat shows a synergistic effect, combination of doxorubicin and cyproheptadine indicates an antagonistic effect, and the combination of vorinostat and cyproheptadine has an additive effect.

Key words : bladder cancer, doxorubicin, vorinostat, cyproheptadine

B025

Molecular characterization of colistin-nonsusceptible Klebsiella pneumoniae isolates in a tertiary teaching hospital

粘菌素不敏感性肺炎克雷白氏菌分離株的分子特徵:南臺灣醫學中心的世代追蹤性研究

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Background: This study aimed to characterize colistin-nonsusceptible *K. pneumoniae* (CoNSKP) isolated from patients with urinary tract infection and bacteremia during 1999 to 2022 in a tertiary teaching hospital in Taiwan.

Methods: A total of 1,966 *K. pneumoniae* were collected. The antimicrobial susceptibility to 19 antibiotics, capsular (K) types, and virulence factor distribution of CoNSKP were determined. Colistin resistance mechanisms were determined by PCR and sequencing of *phoPQ*, *pmrAB*, *mgrB*, and *mcr* genes. Conjugation assay was used to determine the transferability of plasmids carrying *mcr* genes to *K. pneumoniae* ATCC BAA-1706 and *E. coli* C600.

Results: Among the 21 CoNSKP, 12 were multidrug-resistant and four were extensively drug-resistant. Untypable capsular type, K64, and K2, were found in 5, 3, and 2 CoNSKP, respectively. The insertion element IS*5*, IS*903B*, and IS*Vsa5*, were found to inactivate *mgrB* of 1, 1, and 3 CoNSKP isolates, respectively. Moreover, 1, 5, 4, 13, and 1 missense mutations of PhoP, PhoQ, PmrA, PmrB, and MgrB were identified in 21 CoNSKP. Only two isolates SC-KP169 and SC-KP585 carried *mcr-1* and *mcr-8*, respectively, determined by Nanopore whole genome sequencing. The plasmid pSC-KP169-1 could be transferred inter- and intra-genus and contributed to the virulence of *K. pneumoniae* to larvae, while the plasmid pSC-KP585-1 could be transferred to *E. coli* but could not affect its virulence to larvae.

Conclusions: We identified 21 CoNSKP from 1,966 isolates and found a conjugative plasmid carrying *mcr-1* gene that contributed to the virulence to larvae of *K. pneumoniae*.

Keywords: colistin resistance, conjugation, *K. pneumoniae*, *mcr*, whole genome sequencing