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慈濟大學



分子生物暨人類遺傳學系

2024 大學生研究成果

壁報展示競賽

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流 程

慈濟大學 分子生物暨人類遺傳學系

2024 大學生研究成果壁報展示競賽

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研究成果壁報展示競賽摘要

The potential pathway of Taiwanese patients in colorectal cancer

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- Background: Colorectal cancer (CRC) is one of the most common malignant cancers in the world. CRC progresses from normal mucosa to adenoma and finally to malignant tumor over time. Currently, the occurrence of CRC involves the participation of many pathways. With the decoding of the human genome and the technological advancement of next-generation sequencing, transcriptomics has become more and more popular. In 2020, Chang Gung Memorial Hospital used 104 Taiwanese CRC patients and transcriptomic analysis to reveal the ethnic basis of the pathogenesis of colorectal cancer in Taiwan. Therefore, in addition to being used for clinical molecular diagnosis of patients, transcriptomics can also be used to classify patients' CRC types and even be used for disease treatment.
- Results: In view of the increasing development of transcriptomics research, therefore, the purpose of this study was to use bioinformatics methods to analyze differentially expressed genes (DEGs) in normal tissues and tumor tissues of 20 Taiwanese CRC patients, and to perform functional analysis of these genes to find potential pathways of the disease, provides mechanistic insights into the nature of the disease. As can be seen in the principal component analysis (PCA) diagram of DEGs, the gene expression of normal tissues and tumor tissues of 20 Taiwanese CRC patients can be clearly divided into two groups. Next, we selected significant ($p_{adj} < 0.05$) and $\log_2\text{FoldChange}$ greater than 1.86 or less than -1.55, and finally selected 990 up-regulated genes and 497 down-regulated genes. Then draw a cluster heatmap for the up-regulated genes and down-regulated genes. Finally, we used GSEA analysis to see which GO terms and KEGG pathways these DEGs participate in. The results showed that the up-regulated DEGs were mostly enriched in DNA binding, cytokine activity, wnt signaling pathway and PI3K-Akt signaling pathway, while the down-regulated DEGs were more related to the regulation of RNA polymerase II.
- Conclusions: Therefore, the results of this bioinformatics analysis provide us with mechanistic insights into the pathogenesis of colorectal cancer. Future research can conduct wet lab experiments on the genes of these two pathways to see if the same situation will occur in colorectal cancer cells.

The role of AQP in colorectal cancer and their potential value

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Colorectal cancer (CRC) is the leading cause of cancer-related death worldwide, and a deeper understanding of its underlying molecular mechanisms is needed to improve treatment strategies. Aquaporin (AQP) is a membrane protein that facilitates the transport of water and other small molecules across cell membranes and has been implicated in various physiological and pathological processes, including cancer. However, the role of AQP in CRC and its response to oxidative stress remains poorly understood.

In this study, we illustrate the involvement of AQP in CRC progression in response to oxidative stress induced by H₂O₂ treatment. First, we analyzed the mRNA and protein expression of AQP5 and AQP8 in CRC cell lines. Our results show differential expression patterns of AQPs compared with normal cells, indicating the potential role of these AQPs in CRC development.

Next, we treated CRC cell lines with different concentrations of H₂O₂ (0, 50, 100 and 200uM) to simulate oxidative stress conditions. The results show the cytotoxic effect of H₂O₂. In addition, we examined the protein expression levels of P53 and P21, key regulators of cell cycle arrest and apoptosis, and found that their expression was increased after H₂O₂ treatment, indicating that the cellular stress response pathway was activated.

Finally, we observed the expression of AQP5 and AQP8 in H₂O₂-treated CRC cells. Our preliminary data suggest that AQP5 and AQP8 expression may be regulated by oxidative stress, although further studies are required to confirm these findings. In summary, our study provides new insights into the role of AQP in CRC and its potential as a therapeutic target for CRC.

Molecular cytogenetic characterization of Polyploid Giant Cancer Cells (PGCCs) in cytarabine-resistant AML cells

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Polyploid giant cancer cells (PGCCs) are known for their multiple nuclei or giant nucleus with extra chromosome sets. They significantly contribute to drug resistance, chromosomal instability, cancer evolution, stem cell properties, and the tumor microenvironment. While PGCCs have been extensively studied in solid tumors and are associated with drug resistance, their role in liquid tumors remains unclear. The treatment of acute myeloid leukemia (AML) often involves chemotherapy, with cytarabine as a key agent in the standard regimen for AML. Despite the clinical curative effect of cytarabine, disease relapse or drug resistance remains a common and unresolved problem. Currently, there are no targeted therapies specifically addressing PGCCs in AML. This study aimed to generate cytarabine-resistant PGCCs and characterize phenotypes and genotypes of drug-resistant PGCCs in AML. We established AML PGCC cell lines from MV4-11 cells via prolonged cytarabine exposure. These cells displayed drug resistance, confirmed by increased viability after cytarabine treatment. Using optical microscopy and cytospin with Liu's staining, PGCCs exhibited a phenotype with a more than three times larger cell size and a giant nucleus. Immunofluorescence staining revealed PGCC characteristics in a subset of drug-resistant cells. Polyploidy analysis using karyotyping, interphase FISH, and flow cytometry indicated a significant rise in polyploid cell populations. Our findings elucidate AML PGCC characteristics, including phenotypes and genotypes. PGCC establishment informs future research on molecular mechanisms, deepening the understanding of liquid tumor biology. These insights may aid in developing targeted therapies for AML patients with PGCC-associated drug resistance.

TCU411 rescued memory deficits in sleep-deprived mice by suppressing GABA_B receptor

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Sleep is an essential biological mechanism for learning and memory formation. Lack of sleep affects working memory, which is linked to the inhibitory GABAergic system by modulating GABA_A and GABA_B receptors. However, many sleeping pills targeting GABA_A receptors have shown several side effects. Therefore, indigenous medicines that are natural, eatable, affordable, and have fewer side effects might be the promising novel therapeutic approach. This study aimed to investigate the effect of TCU411, a Taiwanese indigenous medicine that has been shown to promote sleep, on working memory performance and GABA-related molecules in sleep-deprived (SD) mice. The modified multiple platforms method was used to induce SD for four hours per day, five days consecutively. The locomotor activity, anxiety-like behavior, and working memory were measured after SD. The results demonstrated that mice's locomotor activity and anxiety-like behaviors in SD and SD+TCU411 groups were not altered. Interestingly, SD mice displayed a working memory deficit and were rescued after TCU411 treatment. Subsequently, the expression of GABA_B receptor significantly increased in the hippocampus of SD mice and decreased after TCU411 treatment. This study suggests that TCU411 rescued working memory deficits during SD conditions by inhibiting the overexpression of the GABA_B receptor.

BEST1/4 Expression in Colon Cancer Cells

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Genetic changes in humans can cause many diseases, including cancers. Cancers can occur when genetic changes cause changes in how they grow. Colon cancer is a type of cancer that develops in the colon. This cancer is one of the most common cancers worldwide. A previous study presented data on the differentially expressed genes between tumor and normal tissues of Taiwanese CRC patients. According to the data, the BEST1 and BEST4 genes are downregulated. BEST1 and BEST4 are protein coding genes from bestrophin family. In epithelial cells, this family is believed to form calcium-activated chloride ion channels (CaCCs) and highly permeable to bicarbonate. CaCCs are a diverse group of ligand-gated ion channels for chloride found in various epithelial and endothelial cell types. Sensory transduction, regulation of nervous and cardiac excitability, and secretion of electrolytes and water by epithelial cells are all dependent on CaCCs. Numerous physiological processes, including cell proliferation, migration, and extracellular matrix secretion, are controlled by CaCCs. mRNA levels do not always correlate with protein expression levels because protein expression is regulated by cellular systems. There are additional processes within the cell that influence protein expression. In a recent study, I investigated the mRNA and protein expression of BEST1 and BEST4 in colon cancer cells and compared their expression with that in normal cells. First, I designed forward and reverse primers for PCR to amplify specific DNA targets and analyze the levels of corresponding RNA in colon cancer cells (HCT116, SW480, and HT29 cells) as well as in normal lung cells (MRC5 cells). After extracting RNA and protein from cultured cells, I performed RT-PCR and western blot analysis to assess the expression levels of mRNA and protein for BEST1 and BEST4. In the RT-PCR results, the mRNA expression level of BEST1 varies among HT29, MRC5, HCT116, and SW480 cells. The highest mRNA expression level is HT29, and the lowest is SW480. BEST4 is expressed in HT29 cells. In the western blot results, the protein expression differs between colon cancer cells (HT29, SW480, SW620, HCT116) and normal colon cells (CCD18Co). The expression level of BEST1 protein is higher in HT29 and SW480 compared to SW620, HCT116, and CCD18Co, while the expression level of BEST4 protein is higher in SW480 and HCT116

compared to HT29, SW620, and CCD18Co. Genetic changes can lead to various diseases, including cancer, such as colon cancer, one of the most prevalent worldwide. Recent research on colon cancer cells' mRNA and protein expression, compared to normal cells, revealed differential levels of BEST1 and BEST4 genes, suggesting potential implications for cancer development and treatment.

***Zanthoxylum ailanthoides* Demonstrates Anti-Leukemia Effects in Core Binding Factor Acute Myeloid Leukemia (CBF-AML) Kasumi-1 Cells**

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Core binding factor AML (CBF-AML) represents a subtype of AML characterized by specific chromosomal alterations, primarily the presence of t(8;21)(q22;q22), leading to the formation of oncogenic AML1-ETO (RUNX1-RUNX1T1) fusion genes implicated in leukemia development. The tender leaves of *Zanthoxylum ailanthoides* have long been utilized as both a dietary supplement and herbal medicine. In this study, we explored the anti-leukemia effects of ethanol extracts of *Zanthoxylum ailanthoides* leaves (ZAE) on Kasumi-1 cells, a CBF-AML cell line. Our findings indicate that ZAE significantly diminishes the viability of Kasumi-1 cells in a time- and dose-dependent manner. Moreover, ZAE induces cell cycle arrest in the G1 phase, triggers cell apoptosis, and fosters monocytic differentiation in Kasumi-1 cells. Gene expression analysis reveals that ZAE downregulates both the AML1-ETO and c-KIT oncogenic genes in Kasumi-1 cells. Additionally, we assessed the cytotoxic activities against Kasumi-1 cells of reported bioactive compounds found in *Zanthoxylum ailanthoides*. Taken together, our data offer novel insights into the potential of ZAE for the chemoprevention or chemotherapy of CBF-AML.

Keywords: CBF-AML, AML1-ETO, *Zanthoxylum ailanthoides*, Kasumi-1, c-KIT

Neuroprotective Effects of *Zanthoxylum ailanthoides* on Anti-Inflammatory Activities in Microglial Cells

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Neuroinflammation constitutes a pivotal process in neurodegenerative conditions like Alzheimer's disease, Parkinson's disease, and dementia. Traditionally, the tender leaves of *Zanthoxylum ailanthoides* have been employed both as a dietary supplement and herbal remedy. This study aims to explore the neuroprotective effects and underlying mechanisms of ethanol extracts of *Zanthoxylum ailanthoides* leaves (ZAE) against LPS-induced inflammation in BV2 microglia cells. MTT assay results indicate that ZAE (18.75-150 µg/mL) does not induce cytotoxicity in BV2 microglia cells. ZAE notably diminishes LPS-induced nitric oxide (NO) production and suppresses LPS-mediated inducible nitric oxide synthase (iNOS) gene expression in BV2 cells. Additionally, ZAE significantly mitigates LPS-induced proinflammatory cytokine expression, including interleukin-1 (IL-1), IL-6, and TNF- α at both mRNA and protein levels in BV2 microglia. These findings suggest that ZAE exhibits anti-neuroinflammatory activity, presenting a potential neuroprotective agent for the prevention or treatment of neurodegenerative disorders.

Keywords: Neuroinflammation, *Zanthoxylum ailanthoides*, microglia, iNOS, TNF- α

AQP0 plays an important role in erythropoiesis

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Erythrocytes, the most prevalent cells in human blood, are pivotal in oxygen transportation throughout the body. Therefore, diagnosing and treating dyserythropoiesis in patients is crucial for their overall health. Aquaporins, a family of small transmembrane proteins, function as water channel proteins. Currently, 13 homologs have been identified, expressed in various tissues and cells with differing patterns throughout the body. Among these, aquaporin 0 (AQP0) was exclusively expressed in lens fiber cells, testicular Leydig cells, and Sertoli cells. However, a paper published by our laboratory in 2021 unveiled that AQP0 acts as a surface protein in early erythroid cells within the bone marrow, absent in non-erythroid blood cell types. Notably, in the bone marrow of individuals with erythropoiesis disorders, early erythroblast cells exhibited lower AQP0 expression levels compared to those in healthy individuals. This discovery suggests a potentially significant role of AQP0 in erythropoiesis. To further explore the association between AQP0 and erythropoiesis, we aim to employ an erythroid differentiation cell model to knock down AQP0 using the short hairpin RNA (shRNA) technique.

Characterization of potential receptors of dengue virus non-structural protein 1 on human erythroleukemia cells

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Dengue fever is an illness caused by the dengue virus (DENV), affecting over 400 million individuals annually, with no current effective treatment available. A distinctive symptom of DENV infection is thrombocytopenia. Previous research has demonstrated that the virus induces thrombocytopenia by either impeding the production of megakaryocytes or interacting with platelets, leading to their activation. Studies have revealed that the non-structural protein 1 (NS1) of the DENV in patients' blood binds to platelet surface receptors, triggering their activation and subsequent clearance by immune cells. A recent research report from our laboratory highlighted that the NS1 protein may impede megakaryocyte differentiation or induce death. As the precursor cells of platelets, megakaryocytes consequently lose their ability to produce platelets, typically reducing the platelet count in the bloodstream. Currently, the identity of the receptor for DENV-NS1 on the surface of human blood precursor cells or megakaryocytes remains unclear. Therefore, this study aims to identify the NS1 receptor located on the surface of human erythroleukemia cells. If the results align with expectations, this specific NS1 protein receptor could serve as a potential target for the future development of dengue fever therapeutics.

Assessment of Intestinal Damage Due to Psychological Stress in Mice

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Acute psychological stress significantly affects the gastrointestinal tract, often leading to conditions such as intestinal ulcers and increased permeability. The detailed mechanisms underlying these stress-induced effects are not fully understood. This study aims to examine the impact of acute restraint stress on intestinal damage in mice and to quantify this damage using a specific biomarker. The experimental design involved dividing mice into groups subjected to either restraint stress or no stress as controls. The severity of intestinal damage was assessed by measuring the concentration of Evans blue dye, which leaks from the intestine and enters the plasma, serving as an indicator of intestinal permeability and damage.