上海交大——高医大生物医学论坛

2017年5月23日 论坛议程

交大医学院懿德楼 101 会议室

第一部分 开幕致辞

09:15-09:20 上海交大医学院领导致欢迎词（陈红专副院长）
09:20-09:25 高雄医学大学领导致辞（刘景宽校长）
09:25-09:30 双方领导互换礼物、合影留念

第二部分 科研演讲 *(演讲 20 分钟，讨论提问 5 分钟)*

09:30-09:55	**颜正贤** 高雄医学大学医学院院长 / 临床医学研究所教授 演讲题目： Genetics and Epigenetics of Systemic Lupus Erythematosus in Taiwan
09:55-10:20	**沈南** 上海交通大学医学院附属仁济医院风湿科，上海风湿病学研究所科主任，所长 / 主任医师，教授 演讲题目： New Insight Into MicroRNAs Directed Molecular Pathways linked to Immune Dysregulation in Autoimmune Diseases
10:20-10:45	**邱世欣** 高雄医学大学附设医院小儿血液肿瘤科主任 / 医学系小儿学科教授

	演讲题目： GPR 177 expression regulates exosome secretion in cancer metastasis
10:45-11:05	茶歇
11:05-11:30	**王侃侃** 上海交通大学医学院附属瑞金医院上海血液研究所/医学遗传学国家重点实验室教授，医学遗传学国家重点实验室首席研究员 演讲题目： Deciphering the regulatory mechanisms of acute myeloid leukemia by genomic approaches
11:30-11:55	**洪志兴** 高雄医学大学小港医院小儿科主任 / 教学研究中心主任 / 医学系小儿学科教授 演讲题目： 环境荷尔蒙对人类树突细胞功能影响之机制研究
12:00-13:25	工作午餐（科教楼 13 楼，聚馨阁）
13:30-13:55	**叶菱秀** 上海交通大学医学院、上海市免疫学研究所　研究员 / 正高级 演讲题目： Influence of DNA Sequence on Antibody Somatic Hypermutation
13:55-14:20	**田育彰** 高雄医学大学研究发展处行政规划组组长 / 健康科学院医学影像暨放射科学系教授 演讲题目： 以蛋白质体学发展疾病治疗新策略 :癌症标靶治疗微胞药物开发-辐射增敏剂应用于欧杰电子治疗之研究

14:20-14:45	**余健秀** 上海交通大学医学院生物化学与分子细胞学系 教授 演讲题目： Protein modifications control cancer progression by regulating microRNA biogenesis and efficiency
14:45-15:05	茶歇
15:05-15:30	**郭柏麟** 高雄医学大学附设医院临床医学研究部基因体及蛋白质体医学研究室主任 / 临床医学研究所教授 演讲题目： 从肿瘤微环境探究至治疗模式发展
15:30-15:55	**陈生弟** 上海交通大学医学院附属瑞金医院神经科 所长 / 教授、主任医师 演讲题目： Erk1/2-Elk-1 Dependent Expression of SOD1 Played a Crucial Role in the anti-oxidant Function of DJ-1

发言人简介与发言摘要

姓　　名： 颜正贤

职务/职称： 高雄医学大学临床医学研究所教授
医学院院长

工作部门： 高雄医学大学附设医院过敏免疫风湿科

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研究领域： Immunogenetics

研究经历与研究内容：

长期以来的研究兴趣是探讨 rheumatoid arthritis 之 etiopathogenesis。过去的研究以 immunogenetics 为主，近年研究方向则偏向 epigenetics。另外，目前正探讨 virus 在 RA 之 pathogenesis 所扮演的角色。

演讲题目：Genetics and Epigenetics of Systemic Lupus Erythematosus in Taiwan

演讲摘要：

Genes and their epigenetic modifications play some roles in the pathogenesis of SLE. Genes may be related to the susceptibility, clinical manifestations, and severity of SLE. In Taiwan, *HLA-DMA* 0104, *PD-L2* 47103T, *PD-1* 7209C, *OSMR* -100T, *IκBα* -826T and *CYP1A1* 4887A were associated with susceptibility to SLE.

Concerning the clinical manifestations, *IκBα* -881G was associated with the occurrence of vasculitis in SLE. *IκBα* -550T might be a protective factor for the development of malar rash. SLE patients with thrombocytopenia had a lower frequency of SOCS1-1478del compared with patients without thrombocytopenia. *CYP1A1* 4887A tended to be associated with the occurrence of renal involvement in SLE patients.

Methylation and hydroxyl-methylation of DNA are epigenetic modifications of genes. The patients with SLE had a significantly lower level of DNA methylation in PBMC than the controls. The expression of both DNMT1 and MBD2 mRNA was significantly increased in the SLE patients compared with the controls. We also found a positive correlation between DNMT1 and MBD2 mRNA levels in the patients with SLE. The SLE patients had higher methylation in the *HDAC6* promoter and lower HDAC6 mRNA expression than the controls. These changes may be related to the susceptibility of SLE. However, they are not associated with the disease activity of SLE.

TETs are involved in the hydroxyl-methylation of 5-mC. The expressions of TETs and 5-hmC level in the PBMC of SLE patients will be presented.

姓　　名：沈南

职务/职称：科主任，所长/主任医师，教授

工作部门：上海交通大学医学院附属仁济医院风湿科
上海风湿病学研究所

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研究领域：系统性红斑狼疮等自身免疫病的发病机理及靶向治疗研究

研究经历与研究内容：

曾先后在美国 UCLA 大学风湿病学中心、荷兰阿姆斯特丹大学医学中心学习进修，并获得阿姆斯特丹大学博士学位。主要从事系统性红斑狼疮的发病机理及靶向治疗研究，近年来通过功能基因组学、细胞及分子免疫学等多种策略在 SLE 关键性致病通路的研究中取得显著进展：1）率先发现 I 型干扰素通路异常激活是狼疮病人的主要分子表型；2）系统性阐述 I 型干扰素通路过度活化对狼疮免疫病理损伤的细胞及分子机制；3）揭示红斑狼疮 I 型干扰素通路异常激活的遗传机制；4）阐明了 miRNA 在狼疮关键致病通路中的重要调节作用。在 Nature Medicine、Nature Genetics、Immunity、Plos Genetics、Blood、PNAS、J Immunol 等杂志上发表 SCI 收录论文 100 余篇。

演讲题目：New Insight Into MicroRNAs Directed Molecular Pathways linked to Immune Dysregulation in Autoimmune Diseases

演讲摘要：

The disorder of fine regulation of gene expression can cause complex diseases' phenotypes. Recently microRNAs have emerged as a major class of gene expression regulators linked to most biological functions. Dysregulation of miRNAs has been described in various disease

states,including severalautoimmune diseases.The roles of dysregulated miRNAs in SLE pathogenesis are just beginning to be uncovered.

First, miRNA expression profiling studies based on lupus patients' blood cells, body fluid and target tissues have revealed unique miRNA signatures as well as their associations with disease activity and major organ involvements, suggesting miRNAs as potential biomarkers for the disease assessment of lupus patients. Moreover, a series of in vitro studies has recently unveiled novel cellular and molecular mechanisms underlying roles of miRNAs in SLE disease processes including their functions in control of IFN pathway activation, inflammatory mediator production and DNA methylation state of T cells as well as their interaction with disease relevant genetic variants. During the past several years, we have shown that miRNAs singly or synergistically activate abnormal immune and inflammatory pathways, leading to pathological lupus autoimmune responses. More importantly, modulating these abnormal miRNAs restores normal immune function in in vitro cell culture. We thus hypothesize that in vivo manipulation of these miRNAs expression could regulate major inflammatory signaling pathways linked to lupus tissue damage and the approach to correct these dysregulated miRNAs should reverse lupus major phenotypes. Recently we have been evaluating the capacity of selective miRNA inhibition to cure lupus in murine models, as preparatory experiments before advocating human trials using this approach. We have applied gene knockout, transgenic and bone marrow chimeric mice, as well as chemically synthesized

miRNA mimics and inhibitors, to study the role of miRNAs in inducing lupus-related pathological tissue damage. We also determined the potential for reversing disease and evaluate efficacy, while also elucidating the miRNA-related molecular mechanisms of lupus pathogenesis. We believe the results of these experiments would prepare our community of lupus investigators and pharmaceutical scientists to exploit this exciting new technology toward ending the suffering caused by lupus and other autoimmune diseases.

姓　　名：邱世欣

职务/职称：主治医师/主任

工作部门：高雄医学大学小儿部血液肿瘤科

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研究领域：儿童血液肿瘤，白血病

研究经历与研究内容：

长期在儿童血液肿瘤科从事临床工作，早期研究以临床疾病治疗与基因变异为主。近年来在儿童白血病领域除了临床治疗研究外，并进入致病机转研究，研究重点在 Wntless 于儿童急性淋巴性白血病细胞的生物调控机转及临床预后。

演讲题目：GPR 177 expression regulates exosome secretion in cancer metastasis

演讲摘要：

Cancer directly affects at least one-third of the human population. Despite this extensive research prevalence, the genetic determinants of cancer risk remain largely unknown. Highly potent mutations of proto-oncogenes as well as tumor suppressor genes, and more subtle and complex micro environmental interactions within tumor and stromal cells are currently thought to influence susceptibility to cancer. Wntless/Evi/Sprinter/GPR177, a newly identified conserved seven-pass transmembrane protein, is an essential regulatory retromere protein required for exocytosis of the Wnt proteins. Loss-of-function of Wntless in mice causes embryonic lethality due to disruption of the axial patterning. Over expression of Wntless has recently reported in several

human cancer, such as glioma, breast cancer and BCP ALL, and consequently, increases the cell proliferation and regulates the tumorigenic activity and progress. However, the detailed regulatory pathway and the pathological role of Wntless are still unclear. Through Wntless mutant mice and cancer cell lines, it was suggested the over expression of Wntless up regulated exosome' s markers, e.g. CD9, CD63, TSG101 and CD81, especially GPC1, in the culture medium. Exosome - specific miRNA, e.g. miRNA 141, 21 and 107, were also shown to up-regulated in the culture medium. Reversely, the down regulation of Wntless in cancer or mutant cells showed to decrease the exosome' s markers. These results showed Wntless expression involved in exosome secretion and consequent tumor micro environmental establishment.

姓　　名：王侃侃

职务/职称：教授

遗传学国家重点实验室首席研究员

工作部门：上海交通大学医学院附属瑞金医院上海血液研究所/医学遗传学国家重点实验室

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研究领域：Molecular Hematology and Systems Biology

研究经历与研究内容：

Dr. Kankan Wang is a Professor of Molecular Hematology and Systems Biology in Rui-Jin Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Dr. Wang received the Bachelor degree of Medicine and the Master degree of Science from Shanghai Medical University, and the Ph. D. degree of Genetics from Shanghai Second Medical University. She continued her training in Functional Genomics in University Health Network, University of Toronto, Canada before she returned to China in 2002. Her group focuses on studying the mechanisms of leukemia using high throughput technologies and developing algorithmic and statistical methods to interpret the biological significance of the diseases. Dr. Wang has published more than forty manuscripts in peer-reviewed journals, including Cancer Cell, Blood, PNAS, Oncogene. She also obtains a United States patent (Patent Number 8, 088, 822) and three software copyrights (Copyright Number: 094524, 122062 and 122082). She received the first prize for the National Nature Science Reward from the Ministry of Education, the

first prize for the Shanghai Scientific and Technological Progress Reward from Shanghai Municipal Government, and was awarded as "New Century Excellent Talents" by the Ministry of Education.

演讲题目：Deciphering the regulatory mechanisms of acute myeloid leukemia by genomic approaches

演讲摘要：

Recent advances in high throughput technologies have facilitated the study of complex diseases such as leukemia from multiple perspectives. Our group is committed to leukemia research with expertise in combining multiple omics technologies and molecular approaches to address crucial questions about transcriptional regulatory mechanisms in the pathologenesis and treatment of leukemia. Using ChIP-seq technologies, we have identified genome-wide binding sites of the PML/RARα and AML1/ETO fusion proteins, which play causal roles in the development of acute myeloid leukemia (AML). The PML/RARα binding profiling demonstrate PU.1 as a previously unrecognized role of cooperating transcription factors in DNA targeting of PML/RARα in acute promyelocytic leukemia (APL). The AML1/ETO binding profiling reveal a novel genome-wide interplay between AML1/ETO and wild-type AML1 in the development of t(8;21) AML. Based on the target genes they identified using the omics technologies, we have further characterized the distinct regulatory features of several key target genes (e.g. PSMBs, TF, CTSG and HCK) of the fusion proteins crucial for the pathogensis of leukemia. In line with the hypotheses derived from

global analysis, we demonstrate that a well-tolerated vitamin A derivative, fenretinide, is capable of eradicating leukemia stem cells in AML. Furthermore, a series of bioinformatics tools have been developed in the laboratory of the applicant to meet the challenge of data mining from the massive amounts of multi-omic data in a more accurate and in-depth manner. These findings enrich our knowledge of understanding the pathogenic and therapeutic mechanisms of AML.

姓　　名：洪志兴

职务/职称：教授/小儿科主任/教学研究中心主任

工作部门：高雄医学大学/高雄市立小港医院

电子邮件：pedhung@gmail.com

研究领域：儿童气喘过敏暨免疫学、表观基因学

研究经历与研究内容：

2000 年	儿童过敏暨免疫专科医师、中华民国过敏暨免疫专科医师
2002-2003年	美国约翰霍普金斯大学(Johns Hopkins university)气喘暨过敏病中心研究员
2003年	儿童过敏暨免疫专科医师之训练老师
2005年	台湾儿童气喘过敏暨免疫学会理事
2005年	高雄医学大学附设中和纪念医院小儿过敏暨免疫科主任
2008年	台湾儿童气喘过敏暨免疫学会理事
2009年	高雄医学大学医学院医学研究所博士毕业
2009年8月	微免感杂志副主编 (Impact Factor: 2.955)
2011年8月	高雄医学大学升等教授 (教字第019256号)
2011年9月	台湾儿童过敏气喘免疫及风湿病医学会副秘书长
2013年	高雄市立小港医院小儿科主任
2015年	中华民国免疫学会常务监事
2016年	高雄市立小港医院教学研究中心主任

获颁台湾儿童过敏气喘及免疫学会研究论文奖: 94、95、 96、97、98、99、100、102、103及105年度(94及103年度为最佳论文奖)。

连续2年获颁台湾儿童过敏气喘及免疫学会海报论文奖: 100及101年度

中华民国免疫学会论文奖: 94、96年度及100年度

高雄医学大学杰出论文奖: 96、97、98、99、100、101及102年度

高雄医学大学研究贡献奖: 99年度

演讲题目：环境荷尔蒙对人类树突细胞功能影响之机制研究

演讲摘要：

儿童过敏及气喘过去几十年间日益增多，过敏及气喘是一种慢性发炎性疾病，近来其盛行率在工业化国家快速增加，特别儿童族群，是儿童最常见的慢性疾病，成为儿童健康的一大威胁。环境荷尔蒙是工业及农业所使用的化合物在环境中的衍生物，结构类似人体的荷尔蒙，会干扰人体的内分泌、生殖系统及免疫系统，可能与过敏及气喘疾病形成有关。在台湾环境荷尔蒙/塑化剂之滥用严重，甚至有厂商将塑化剂邻苯二甲酸二辛酯(DEHP)(一类环境荷尔蒙/塑化剂)加入饮料当中造成几年前的「塑化剂风暴」，造成食品安全危机。环境荷尔蒙的暴露及其对儿童过敏及气喘疾病之影响，以及其致病机制仍未知。过敏气喘的成因可能与树突细胞之不当免疫反应有关，可能也与环境荷尔蒙之曝露不断增加有关。根据我们两篇 IF> 5 的论文(Hung CH, Environmental Health Prospectives 2010; 118: 67-72. IF=7.036) ; Allergy 2013; 68:870-9 (Impact Factor = 5.883) ,发现环境荷尔蒙/塑化剂可经过表基因(epigenetics)调控影响人类树突细胞，发现骨髓树突细胞激素 TNF - α 之表现是会受表观基因调控 histone 3, 4 acetylation 及 histone H3K4 tri - methylation 的影响。DEHP 可以透过控制表观基因调控来调控人类浆树突细胞之第一型干扰素细胞激素分泌， 包括表观基因 histone modifications 之 histone acetylation 及 H3K4 之 Tri - methylation。环境荷尔蒙刺激后的人类树突细胞会使 T 细胞走向 Th2 而产生过敏反应及疾病，表观基因调控参与其中及相关之作用机转。DEHP 的不良作用可能藉由改变表观基因调控而将 DEHP 影响一代传一代，我们的人类树突细胞研究聚焦环境荷尔蒙特别是塑化剂对表观基因的影响。

姓　　名： Leng Siew Yeap (叶菱秀)

职务/职称： 研究员/正高级

工作部门： 上海交通大学医学院

上海市免疫学研究所

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研究领域： B 淋巴细胞抗体多样化

研究经历与研究内容：

研究员，博士生导师。2010 年获得剑桥大学博士学位；2010-2015 年在哈佛大学波士顿儿童医院 Frederick Alt 实验室从事博士后研究。2016 年加入上海交通大学医学院上海市免疫学研究所，任“抗体多样化”课题组组长。2017 年入选中组部“青年千人计划”。研究兴趣集中在 B 细胞抗体基因在体细胞高频突变过程的分子机制以及广谱中和抗病毒抗体产生的分子机制，相关工作发表于 Cell 等本领域国际期刊和专著。作为第一发明人申请的一项国际专利已获得欧洲专利授权。

演讲题目： Influence of DNA Sequence on Antibody Somatic Hypermutation

演讲摘要：

In order to fight against various pathogens that our bodies encounter daily, B cells produce a large antibody repertoire through processes that involve genomic alterations of the antibody genes sequences. Activated B cells undergo Somatic Hypermutation (SHM), whereby point mutations in the antibody genes results in antibody affinity maturation,

and Class Switch Recombination (CSR), which changes the effector function of the antibody. The processes of SHM and CSR are mediated by Activation-Induced Cytidine Deaminase (AID), a single-stranded DNA mutagenic enzyme.

Our lab is interested in understanding how AID is specifically targeted to the antibody genes and how DNA sequences influence AID activity outcomes. Our research has implications on vaccine strategies to elicit rare antibodies such as, anti-HIV1 broadly neutralizing antibodies, which accumulate extraordinary levels of SHM and often with deletions / insertions.

姓　　名：田育彰

职务/职称：教授

工作部门：高雄医学大学医学影像暨放射科学系

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研究领域： 蛋白质体，医学工程，核子医学，癌症与老化疾病

研究经历与研究内容：

微胶囊表面改质之药物控制释放：利用微胞囊（micelle）形成疏水基在内而亲水基在外之球体微结构，当微胞囊进入液循环时，微胞囊因其具无毒性与易于与水兼容之特性，因此可以避免被网状内皮系统（RES）所辨识或吞噬，并可作为药物之载体；生医材料表面改质：讨论奈米甲壳素与蚕丝表面改质所引发的细胞免疫反应与分泌蛋白分析；肿瘤蛋白生物标记之研究：主要是针对癌症的生物标记的新发现，尤其是肝癌、乳癌与大肠癌等国人常见的疾病做相关的研究并提出可能的肿瘤标记与转移路径。发明专利“一种阿兹海默症之分子指标”已获专利证书。2007-2010年间参与国际研究合作计划The Asia Oceania Human Proteome Organisation Membrane Proteomics Initiative，计划总主持人为Prof. T. William Jordan（Centre for Biodiscovery and School of Biological Sciences, Victoria University of Wellington, Wellington, New Zealand）并于2010年共同发表文章于Proteomics期刊。承续该研究于2014年参与执行HUPO Chromosome-based Human Proteome Project（C－HPP），计划总主持人为Prof. Young - Ki Paik（Yonsei Proteome Research Center, Yonsei University, Seoul, Korea），台湾地区计划总联络人

为中央研究院化学所陈玉如所长，研究主题为以胚胎发育组织探讨人类第四号染色体遗失蛋白质的功能。

演讲题目：以蛋白质体学发展疾病治疗新策略：癌症标靶治疗微胞药物开发-辐射增敏剂应用于欧杰电子治疗之研究

演讲摘要：

聚合物微胞为一具可溶性之双性分子链所组成，本研究以 hydrophilic poly (ethylene glycol) 及 hydrophobic poly (ε – caprolactone) (PEG – PCL) 聚合微胞为基材，微胞表面加以玻尿酸或 CD44 抗体修饰，增进其对肿瘤组织之亲和性。实验以微胞作为药物载体，并尝试包覆放射性同位素之癌症治疗剂 Iododeoxyuridine (IUdR)， 以探讨维持放射药物之长效性与减低药物之副作用的可行性。IUdR 是核苷类似物，肿瘤治疗的新方法是利用 IUdR 中的碘以低剂量 X 光诱导欧杰电子， 使其破坏肿瘤细胞 DNA 双股结构，进而造成细胞凋亡。本实验提出了欧杰电子治疗在动物模式中的应用及证实包覆放射性同位素之癌症治疗剂微胞在肝脏肿瘤治疗或造影的发展与应用具有较高的潜力。

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研究领域： 蛋白质修饰调控非编码 RNA 与肿瘤

研究经历与研究内容：

余健秀，男，博士，现任上海交通大学医学院特聘教授、博士生导师。1990 获华南农业大学学士学位，1996 年、2000 年分别获中山大学动物学与分子生物学硕士、博士学位。2000-2002 年任中山大学副教授。2002~2007 年在美国 Sanford-Burnham Medical Research Institute /UCSD（美国加州大学）从事博士后研究；2007~2008 年任 Sanford-Burnham Medical Research Institute /UCSD，研究员（Staff Scientist）；2008～2009 年任美国纽约大学 NYU Langone Medical Center，研究助理教授。2009 年 9 月至今，任上海交通大学医学院生物化学与分子细胞学系 PI、特聘教授。主要致力于（1）探讨蛋白质修饰在肿瘤发生发展的作用及其分子机制，首次鉴定了 PTEN 的 SUMO 化修饰，发现其直接介导 PTEN 膜结合而抑制肿瘤发生发展，解析了 PTEN-PI3K-AKT 通路的分子机制；（2）蛋白质修饰调控非编码 RNA 生成和代谢的作用机制，其系列研究揭示了由蛋白质修饰介导的非编码 RNA 调控网络和作用方式。如首次发现 miRNA/siRNA 作用效率受控于 TARBP2 的 SUMO 化修饰程度，Ago2 的乙酰化修饰可以调控 miRNA 前体在 miRISC 复合物上的招募而改变 miRNA 表达谱等。已在国际著名学术期刊 Molecular Cell, Nature Communications, EMBO J,Nucleic Acids Research 等发表研究论文 50 多篇 ,先后被引用 1400 多次，有 3 篇文章被 Faculty 1000 推荐。

主持国家自然科学重点、重大研究计划、面上项目以及国家科技部重大项目子项目等课题十多项，任国家自然科学基金医学部二审专家。

演讲题目：蛋白质修饰调控非编码 RNA 与肿瘤 Protein modifications control cancer progression by regulating microRNA biogenesis and efficiency

演讲摘要：

MicroRNAs (miRNAs) that are important regulators involved in diverse physiologic and pathologic processes including cancer. Post-translational modifications (PTMs) of key proteins (Ago2, Drosha, Dicer, TARBP2, DGCR8, KHSRP *etc.*) play important functions in regulation of miRNA biogenesis and RNA-induced gene silencing. However, it is not clear how PTMs to regulate biogenesis and function of miRNAs.

We recently found that (1) TARBP2 SUMOylation did not influence the biogenesis of mature miRNAs, but it enhanced the gene-silencing efficiency of miRNAs and suppressed tumor progression. (2) DGCR8 SUMOylation majorly occurred at two sites K707 and K259. K707-SUMOylation of DGCR8 increased its affinity with pri-miRNAs and directed the function of pri-miRNAs in oncogenic gene silencing, which promoted tumorigenesis and tumor cell migration. On the contrary, K259-SUMOylation of DGCR8 promoted by the tumor suppressor p14ARF mainly maintained its nuclear localization to function as a partner of Drosha in the MC complex, which prevented the aberrant miRNA biogenesis and exerts its tumor-suppressive function. (3) We also discovered that SUMOylation of KHSRP impaired the processing step of pre-miRNAs from pri-miRNAs which harbor G-rich stretches in their terminal loops, resulting in the downregulation of a subset of

miRNAs such as let-7 family and subsequent tumorigenesis. (4) Excitingly, we demonstrated that Ago2 acetylation controlled the pre-miRNA deposits in miRLC thereby altering the global miRNA expression profile, and our studies provided a novel mechanism on miRLC (miRISC loading complex) formation and miRNA biogenesis regulated by Ago2 acetylation.

Therefore, our above results suggest that PTMs have key roles in regulation of both biogenesis and efficiency of miRNAs.

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研究经历与研究内容：

个人研究主要是探讨肺癌肿瘤微环境，包括肺癌细胞如何躲避免疫细胞之监控，以及肺癌细胞又如何透过免疫细胞进而促进癌之恶化；除此，亦进行肺癌骨转移模式之分析，并找出其可能的分子机制。研究整合基础及临床，探讨目前所遭遇的瓶颈，不仅微观地了解肺癌细胞的特性，亦巨观地探讨肺癌细胞与周遭细胞(免疫细胞及骨细胞)的交互作用。

演讲题目：从肿瘤微环境探究至治疗模式发展

演讲摘要：

在肺癌微环境的研究，我们发现半乳糖凝集素-1 (galectin-1)在肺癌细胞株和肺癌病人血清及组织检体都有很高的表现，研究结果发现肺癌细胞分泌了galectin-1 抑制了单核细胞衍生树突细胞(monocyte-derived dendritic cells; MdDCs)，并且干扰了 T 细胞的反应以及造成了 Tregs 的增加；更甚之，将galectin-1 阻断的肺癌细胞移植至老鼠，则 IL-10 的表现量降低，研究结果推测 galectin-1 及 IL-10 的主轴是肺癌引起免疫抑制的关键因素。除此，我们也发现肿瘤相关树突细胞(tumor associated dendritic cells; TADCs)衍生的双调蛋白(amphiregulin)透过旁泌地增加肺癌细胞增生、移行及上皮间质转化

(epithelial-mesenchymal transition; EMT)，这些发现也揭露树突细胞浸润在肿瘤会表现出大量的 amphiregulin；更甚之，若老鼠给予 anti-amphiregulin antibodies，则会降低癌症恶化以及增加存活率，推测 amphiregulin 在树突细胞及癌细胞的交互作用是一新颖角色。有关肺癌与树突细胞之间的复杂性，我们又发现 TADCs 与肺癌交互作用的另一个机制，肺癌分泌 galectin-1 诱导 TADCs 产生解整合素样金属蛋白酶 9/17 (a disintegrin and metalloproteinase 9/17; ADAM9/17)，然后裂解肝素结合表皮生长因子样生长因子(heparin-binding EGF-like growth factor; HB-EGF)， 接续透过旁泌作用促进癌之恶化；更甚之，我们也侦测到 HB-EGF 表现在 CD11C DCs 所浸润的老鼠肿瘤组织之中，这些发现证实 HB-EGF 在肿瘤微环境中扮演重要的角色。

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研究经历与研究内容：

长期从事神经变性疾病诊治的基础与临床研究，主要围绕氧化应激、免疫炎症、蛋白酶体功能紊乱与帕金森病的发病机制、帕金森病早期诊断的生物标志物、合成性药物、中药及干细胞治疗，以及非药物治疗的研究。获得国家及省部级科技进步奖 28 项，发表 SCI 论著 190 余篇。主编 15 部教科书或专著，以及主持制定了 10 多项帕金森病及相关疾病额诊断标准及治疗指南。

演讲题目：Erk1/2-Elk-1 Dependent Expression of SOD1 Played a Crucial Role in the anti-oxidant Function of DJ-1

演讲摘要：

Parkinson’ s disease (PD) is a common neurodegenerative disease which affects approximately 1% among persons 65 years of age and 5% among those 85 years or older. The featured pathological change of PD is the selective and progressive loss of dopaminergic (DA) neurons, but the molecular mechanism underlying the neuronal death still has not been clarified. Nevertheless, increasing evidences suggest that both

environmental and genetic factors play important roles in the pathogenesis of the disease.

Epidemiologic studies implicated that increased incidence of PD is associated with overexposure to environmental factors such as iron, manganese, herbicides and pesticides. These neurotoxins are believed to induce oxidative stress, which is thought to be a significant cause of Parkinson's disease. Studies in hereditary PD revealed that genetic factors also play an important role in the development of PD. More than 13 loci and 9 genes have been identified to date. Among these genes *DJ-1* has attracted a lot of attention recently because of its association with both autosomal recessive early-onset PD and sporadic PD.

Loss of function mutations of Park7/DJ-1 gene increases the susceptibility of dopaminergic cells to reactive oxygen species (ROS) and causes early-onset familial Parkinsonism. But the mechanisms underlying dopaminergic neurons loss related to DJ-1 mutation remain undefined. Therefore, it is important to find the new mechanisms underlying the anti-oxidative functions of DJ-1.

Bioinformatics analysis reveals that there are several potential Elk-1 binding sites in superoxide dismutase 1 (SOD-1) promoter. In the present study, we demonstrated that DJ-1 interacts with ERK1/2 and is required for the nuclear translocation of ERK1/2 upon oxidative stimulation. The translocation of ERK1/2 can activate Elk-1 and sequentially promote SOD-1 expression. We further demonstrated that

the nuclear translocation of ERK1/2, the activation of Elk-1 and the ensuing up-regulation of SOD-1 are all suppressed in DJ-1 knock-down cells and DJ-1 null mice. Our studies suggest that DJ-1 regulates SOD-1 expression through ERK1/2-Elk-1 pathway in its protective response to oxidative insult. These findings have important implications in understanding of the biology of DJ-1 and its role in the pathogenesis of Parkinson's disease.