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[ST1-"L'Oreal-UNESCO Award For Women in Science"Award Lecture]

Bioplastic production by metabolically engineered bacteria

So Young Choi, Sang Yup Lee

KAIST, Department of Chemical and Biomolecular Engineering

Microorganisms produce diverse polymers for various purposes such as storing genetic information, energy, and reducing power, and serving as structural materials and scaffolds. Among these polymers, polyhydroxyalkanoates (PHAs) are microbial polyesters synthesized and accumulated intracellularly as a storage material of carbon, energy, and reducing power under unfavorable growth conditions in the presence of excess carbon source. PHAs can be biodegraded and possess the material properties that can be widely used for daily plastic products such as bottles, packaging, and also medical applications. Thus, they have received a great deal of attention as sustainable alternatives to petroleum-based synthetic plastics. Through systematic genetic engineering, we have developed several bacterial strains producing non-natural types of PHAs which opened a new avenue toward sustainable production of more diverse plastics. [This work was supported by the Technology Development Program to Solve Climate Changes on Systems Metabolic Engineering for Biorefineries from the Ministry of Science and ICT through the National Research Foundation (NRF) of Korea (NRF-2012M1A2A2026556 and NRF-2012M1A2A2026557)].

Keyword: Metabolic engineering, Biotechnology, Microorganism, Bioplastic, PLA, PLGA

Research Field: Metabolic engineering, Biotechnology, Microbiology

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[ST1-"L'Oreal-UNESCO Award For Women in Science"Award Lecture]

Evolution of targeted therapy in lung cancer - clinical unmet needs and future perspectives

Sun Min Lim

Yonsei Cancer Center

Lung cancer is one of the most common cancer in the world. In 2018, there were over 2 million new cases of lung cancer and over 1.7 million deaths were attributed to lung cancer. Targeted therapy has emerged as an important mean of the disease management for patients with non-small-cell lung cancer (NSCLC). Therapeutic decisions should be guided by an understanding of the molecular features of patient's tumor tissues. The essence of precision medicine is to achieve the goal of "individualized treatment" through genotyping of patients and targeted therapy. At present, the pathogenic genes of NSCLC have been studied most thoroughly and targeted therapy based on genotyping has been the most successful. Herein, I review and analyze recent literature, discuss the targeting pathways and ongoing clinical trials in lung cancer.

Keyword: Lung cancer

Research Field: Lung cancer, targeted therapy, immunotherapy

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[ST1-"L'Oreal-UNESCO Award For Women in Science"Award Lecture]

Ciclopirox inhibits Hepatitis B Virus secretion by blocking capsid assembly

Jung-Ah Kang[1,4], Songwon Kim[1,4], Minji Park[2], Hyun-Jin Park[1], Jeong-Hyun Kim[1], Sanghyeok Park[1], Jeong-Ryul Hwang[1], Yong-Chul Kim[1], Yoon Jun Kim[3], Yuri Cho[2], Mi Sun Jin[1] & Sung-Gyoo Park[1]

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Chronic hepatitis B virus (HBV) infection can cause cirrhosis and hepatocellular carcinoma and is therefore a serious public health problem. Infected patients are currently treated with nucleoside/nucleotide analogs and interferon α, but this approach is not curative. Here, we screen 978 FDA-approved compounds for their ability to inhibit HBV replication in HBV expressing HepG2.2.15 cells. We find that ciclopirox, a synthetic antifungal agent, strongly inhibits HBV replication in cells and in mice by blocking HBV capsid assembly. The crystal structure of the HBV core protein and ciclopirox complex reveals a unique binding mode at dimer-dimer interfaces. Ciclopirox synergizes with nucleoside/nucleotide analogs to prevent HBV replication in cells and in a humanized liver mouse model. Therefore, orally administered ciclopirox may provide a novel opportunity to combat chronic HBV infection by blocking HBV capsid assembly.

Keyword: hepatitis B virus (HBV), Ciclopirox

Research Field: hepatitis B virus (HBV) inhibitor

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International Conference 2021
LIFE
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[ST2-Emerging Opportunities for Drug Discovery on Infectious Diseases]

Drug Discovery for NTDs and Global Pandemics

Charles Mowbray

DNDi

The Drugs for Neglected Diseases initiative (DNDi) exists to serve the needs of neglected patients suffering from neglected tropical and infectious diseases and has already successfully delivered 8 new treatments impacting millions of lives. We have also developed considerable experience in applying our model of collaborative, virtual drug discovery working with our partners across the globe and have assembled a portfolio of projects which may lead to further new treatments. This approach will be described and illustrated with examples for Chagas disease and leishmaniasis and newer applications for COVID-19 and AMR.

Keyword: NTDs, Chagas disease, leishmaniasis, SARS-CoV-2, COVID-19, pandemic preparedness

Research Field: Patients' needs focused R&D for infectious diseases

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[ST2-Emerging Opportunities for Drug Discovery on Infectious Diseases]

GARDP: filling gaps in the new antibiotic pipeline.

Laura JV Piddock

Global Antibiotic Research and Development Partnership

The number of drug-resistant infections is outpacing the provision of new antibacterial treatments and causing an increase in human morbidity and mortality. This is a global problem and impacts the health of everyone and economies of countries around the world. Those most affected are babies, children, the elderly, immunocompromised, and those in countries with weak health systems. GARDP's mission is to focus on developing new treatments, safeguarding their responsible use, and ensuring sustainable access. GARDP's activities are on (1) priority populations (newborn babies, children, hospitalized adults impacted by AMR, vulnerable and marginalized populations), (2) WHO critical and high priorities for which new treatments are needed, and (3) priority infections/syndromes (serious bacterial infections, neonatal sepsis, and sexually transmitted infections). GARDP's Research and Development priorities are the clinical and pharmaceutical development of antibiotics and driving sustainable access. GARDP will also fill gaps in the discovery and exploratory research pipeline by working where others are not (e.g., screening of novel libraries, new chemical entities for underexploited targets). GARDP is building a public health-oriented portfolio to deliver its 5 BY 25 goal (5 new treatments by 2025). GARDP's pipeline portfolio includes of new and old antibiotics with several under evaluation or development. This presentation will describe the scientific aspects of GARDP's work.

Keyword: Antibiotic discovery, research, and development

Research Field: Antibiotics

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[ST2-Emerging Opportunities for Drug Discovery on Infectious Diseases]

Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs

Sangeun Jeon†, Meehyun Ko†, Jihye Lee, Inhee Choi, Soo Young Byun, Soonju Park, David Shum, Seungtaek Kim

Institut Pasteur Korea

COVID-19 is an emerging infectious disease and was declared as a pandemic by WHO. Currently, there is no effective therapeutic available for this disease. Drug repositioning represents the only feasible option to address this global challenge and a panel of 48 FDA-approved drugs that have been pre-selected by an assay of SARS-CoV was screened to identify potential antiviral drug candidates against SARS-CoV-2 infection. We found a total of 24 drugs which exhibited antiviral efficacy (0.1 μM < IC50 < 10 μM) against SARS-CoV-2. Among them, two FDA-approved drugs - niclosamide and ciclesonide - were notable in some respects. Using Calu-3 human lung cell line, we also compared antiviral efficacy of the drug candidates and found nafamostat is the most potent antiviral therapeutic option. In the near future, these already FDA-approved drugs could be further developed following clinical trials in order to provide additional therapeutic options for patients with COVID-19.

Keyword: COVID-19, SARS-CoV-2, Drug repositioning

Research Field: Virology, Infectious disease, Drug development

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[ST2-Emerging Opportunities for Drug Discovery on Infectious Diseases]

Development of Anti-RNA Virus Nucleosides

Lak Shin Jeong

Seoul National University

RNA viruses are often highlighted as the most common class of pathogens behind new human diseases, with the rate of 2 to 3 new viruses being identified each year such as ongoing outbreak of coronavirus disease 2019 (COVID-19). Over the past years, outbreaks of a number of emerging positive-stranded RNA (+RNA) viruses, such as the severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), Chikungunya virus (CHIKV), and Zika virus (ZIKV) have seriously threatened human health. However, antiviral therapy is still lacking for most of these viruses. Thus, it is desirable to develop new antiviral agents for the treatment of viral diseases caused by RNA viruses.

Nucleos(t)ide analogues have a long history in the development antiviral therapeutic agents. A variety of carbocyclic adenosine analogues with antiviral activity, including naturally occurring aristeromycin and neplanocin A are assumed to exert their antiviral action via the inhibition of cellular S-adenosylhomocysteine (SAH) hydrolase. Therefore, SAH hydrolase has been recognized as potential pharmacological target for the development of new antiviral agents. Although neplanocin A and aristeromycin act as potent inhibitors of SAH hydrolase, their therapeutic utility is limited, because of their significant toxicity. Thus, in search of less toxic and more potent inhibitor of SAH hydrolase, the 6′-fluorinated aristeromycin and 6′-fluorinated-5′-homo-aristeromycin were designed, synthesized and evaluated for their antiviral activity against various RNA viruses. Among these, 6′,6′-difluoro-aristeromycin exhibits potent antiviral activities against COVID-19, MERS-CoV, SARS-CoV, ZIKV, and CHIKV. In addition, 6′-β-fluoro-homo-aristeromycin showed potent antiviral activity (EC50 = 0.12μM) against the CHIKV, without noticeable cytotoxicity up to 250μM. It was identified that the introduction of a fluorine at the 6′-position enhanced the inhibition of SAH hydrolase and the activity against RNA viruses. Design, synthesis and antiviral data of carbocyclic nucleosides will be presented in detail.

Keyword: Nucleoside, RNA virus, Antiviral, SAH hydrolase, RNA olymerase

Research Field: Nucleoside Medicinal Chemistry

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
BEXCO, Convention Hall, Busan, Korea
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[ST3-Preclinical Trial for COVID19 Infection]

Clinical aspects in COVID19 infected patients and future perspectives

Sun Bean Kim

Korea University College of Medicine, Anam hospital

COVID-19 can rapidly progress to acute respiratory distress syndrome, multiple organ dysfunction/failure including central nervous system alteration, acute kidney injury, cardiovascular failure, liver injury, and coagulopathy reaching to death.

Like other RNA viruses, SARS-CoV-2 is constantly changing through random mutations. Some variant strains of concern can spread easier, cause more severe disease, or may enhance the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or active immunization.

The pathophysiology of COVID-19 indicates that antiviral treatments targeting the virus would be most beneficial in the early phase of infection, which is primarily driven by the replication of SARS-CoV-2, whereas immunosuppressive/anti-inflammatory therapies are likely to be more beneficial during the late phase of the infection, when the disease is driven by an exaggerated immune/inflammatory response to the virus that causes tissue damage.

We're continuously learning more about COVID-10 every day. The best therapeutic agents are still under investigation. However, we finally might seek for solutions against global disaster with thoughtfully navigating the virus.

Keyword: SARS-CoV-2 pathophysiology; COVID-19; Clinical presentation; SARS-CoV-2 variants of concern

Research Field: COVID-19, Immuno-compromised infection, CMV, Transplantation, HIV

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LIFE
May 25(Tue) ~ May 27(Thu), 2021
BEXCO, Convention Hall, Busan, Korea
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[ST3-Preclinical Trial for COVID19 Infection]

History and trial-and-error of antiviral drugs for coronaviruses and animal models used to assess COVID-19 antiviral candidate

Daesub Song

College of Pharmacy, Korea University

Zoonosis from wildlife represents the most significant threat to global health by spillover of zoonotic disease to human population. Passing from members of one species into human population, alien pathogen thrives and spreads among it and finally result in emergence. Currently unknown pathogens to cause human disease could lead a serious international epidemic, as did SARS-CoV, MERS-CoV, influenza and COVID19. The outbreaks have emphasized the critical need for health monitoring of human and animal, and identification of new, potentially zoonotic pathogens in wildlife population as a one-health measure for emerging infectious disease.

Scientific advancements since the emergence of severe acute respiratory syndrome (SARS) in 2002~2003 and Middle East respiratory syndrome (MERS) in 2012 have accelerated our understanding of the epidemiology and pathogenesis of SARS-CoV-2 and the development of therapeutics to treat viral infection. As no specific therapeutics are available for disease control, the epidemic of COVID-19 is posing a great threat for global public health. To provide a comprehensive summary to public health authorities and potential readers worldwide, here we will prepare detailed information about the trial history for development of coronaviruses' antiviral and animal model for validation of antiviral against COVID-19 in One health perspectives.

Keyword: Zoonosis, COVID-19, antiviral, animal model

Research Field: Zoonotic viral diseases, vaccine, diagnosis, nanobiotechnology

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[ST3-Preclinical Trial for COVID19 Infection]

Preclinical Test for Drug Screening and Vaccine Development of SARS-COV

Je Kyung Seong

COVID19 Animal Model Initiative, Korea Mouse Phenotyping Center & College of Veterinary Medicine, Seoul National University, Korea

The pandemic crisis of SARS-COV2 infection need to develop the new drugs and vaccines to cure SARS-COV2 infected patients. The preclinical test is one of essential process for drug screening and vaccine development. Here we reported the establishment of large scale-preclinical test for drug screening and vaccine development of SARS-COV2 using mouse and hamster. For effective response and process to select the candidate drug and vaccine, internet-based apply system for preclinical test of SARS-COV2. Totally 123 candidate drugs and vaccines for SARS-COV2 has been applied and 32 candidates were selected for preclinical test of SARS-COV2 using mouse and hamster. This was fully supported by the Ministry of Science, Technology and ICT. Total 7 animal biosafety level (ABSL3) including Seoul National University Bundang Hospital, Yonsei University College of Medicine, College of Medicine Korea University, International Vaccine Institute (IVI), Konkuk University, and KRIBB are join this project. All standard procedures for preclinical test was determined with being consulted with KFDA and used. 1x10^5 and 1x10^5 concentration of SARS-COV2 were infected to mouse and hamster by intranasal. Seven among tested 32 candidate drugs and vaccines showed positive results for curing and preventing COVID19 infection. To expand the knowledge of COVID19 infection leading to death, RNAseq and proteomic analysis was done in spleen and lung of COVID19-infected K18-hACE2 mouse at day 1,2,5 ad 7 after infection.

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May 25(Tue) ~ May 27(Thu), 2021
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[ST3-Preclinical Trial for COVID19 Infection]

Establishment NHP model on COVID-19 and vaccine evaluations

Ran Gao, Chuan Qin

Institute of Laboratory Animal Sciences, CAMS & PUMC

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused public health crisis. It also impacted social and economic activities greatly. Animal models were developed at the first time for pathogenesis and vaccine research. Prof. Qin Chuan's team from Institute of Laboratory Animal Sciences, CAMS & PUMC, China has established the first NHP model for COVID-19. With these models, pathogenesis of SARS-CoV-2 was studied and drugs, monoclonal antibodies and vaccines were evaluated.

Keyword: COVID-19, NHP model, vaccine

Research Field: Animal models of human diseases

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[SP2-COVID19 and multi-omics study [KNIH Joint Symposium]]

Multi-omics data of COVID-19 patients

Sang-Cheol Kim

Division of Healthcare and Aritificial Intelligence, Korea National Institute of Health(KNIH), Korea

After the breakout of COVID-19 pandemic worldwide, the importance of understanding and monitoring the virus-mediated infections has been well-recognized. A registry of multi-omics datasets of COVID-19 patients would be valuable to help manage the current and future unexpected virus-mediated pandemics. Here, we present a multi-omics registry of datasets corresponding to COVID-19 patients. Including 120 normal, and 300 COVID-19 patients from Korea population, the datasets possess the following information: (1) clinical data (2) physiological profiling data, including immune profiling for 192 cytokines and molecular profiling, and (3) multi-omics data, including WGS, scRNA-seq, bulk BCR and TCR sequencing, COVID-seq, and HLA typing. Particularly, the data of three time points for mild and a maximum of 7 time points for severe patients have been included. The complete datasets, including the clinical and multi-omics data, are also freely available through an analysis platform especially for multi-omics datasets for researchers with the approval to access it. We expect that these multi-omics datasets of COVID-19 patients will not only provide insights to better understand the biology of COVID-19 infection, but also contribute to develop potential methods for its prognosis and treatment.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[SP2-COVID19 and multi-omics study [KNIH Joint Symposium]]

Immune landscape analysis of COVID19

Eui-Cheol Shin

Graduate School of Medical Science and Engineering, KAIST, Korea

Although most severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals experience mild coronavirus disease 2019 (COVID-19), some patients suffer from severe COVID-19, which is accompanied by acute respiratory distress syndrome and systemic inflammation. To identify factors driving severe progression of COVID-19, we performed single-cell RNA sequencing using peripheral blood mononuclear cells (PBMCs) obtained from healthy donors, patients with mild or severe COVID-19, and patients with severe influenza. The patients with COVID-19 had unique hyper-inflammatory signatures across all types of immune cells, particularly in CD8 T cells and classical monocytes. Among CD8 T cells and classical monocytes, the upregulation of TNF- and IL-1β-driven inflammatory responses were observed in patients with COVID-19, whereas type I interferon (IFN-I) and IFN-χ responses were predominant in patients with severe influenza. Next, we compared severe vs. mild COVID-19. IFN-I responses co-occurred with TNF- and IL-1β-driven inflammatory responses in classical monocytes from patients with severe COVID-19, but not with mild COVID-19, which suggests that IFN-I might have an important role in exacerbating TNF- and IL-1β-driven inflammation in the progression to severe COVID-19. This was validated in severe COVID-19 post-mortem lung tissues. Moreover, there was upregulation of a gene module responsible for IFN-induced abrogation of TLR tolerance in monocytes from severe COVID-19, implying that IFN response exacerbates hyper-inflammation in a feed-forward loop. On the basis of this, we propose that IFN-I response plays a pivotal role in exacerbating inflammation in severe COVID-19. A unique molecular footprint of severe COVID-19 revealed by immune landscaping provides insights for improved management of patients with severe COVID-19.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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beyond the pandemic

[SP2-COVID19 and multi-omics study [KNIH Joint Symposium]]

Pathogenic role of humoral immunity in severe COVID-19

Nam-Hyuk Cho

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Despite the worldwide effect of the Coronavirus disease 2019 (COVID-19) pandemic, the underlying mechanisms of fatal viral pneumonia remain elusive. Here, we conducted kinetic profiling of respiratory viral loads, specific antibody responses, and complement activation to show that severe COVID-19 is associated with enhanced humoral immune responses when compared to mild cases. Enhanced antibody responses and complement activation was associated with disease pathogenesis as evidenced by formation of immune complexes and membrane attack complexes in airways and vasculature of lung biopsies from a fatal case, as well as by enhanced hallmark gene set signatures of FcγR signaling and complement activation in myeloid cells of respiratory specimens from severe COVID-19 patients. We also observed expression of viral antigen in lung epithelial and endothelial cells without producing viruses during late stage of COVID-19, indicating abortive viral infection which may further fuel antibody responses and aggravate immune-complex-mediated inflammation. These results suggest that severe COVID-19 may be pathologically associated with specific humoral immune responses, including enhanced antibody and complement-mediated pneumonic insults, which might be crucial drivers of severe pneumonia in COVID-19 patients.

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International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[SP2-COVID19 and multi-omics study [KNIH Joint Symposium]]

Deciphering B cell receptor repertoires of COVID-19 patients

Junho Chung

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Targeted sequencing on B cell receptor (BCR) of peripheral blood B cells provided BCR repertoire snapshot of COVID-19 patients. Rapid class-switching of BCR clonotypes to other subtypes from IgM with lagged accumulation of somatic hypermutation was observed in both the whole BCR repertoire and virus receptor binding domain (RBD) specific clonototypes, which was previously observed among the patients experiencing severe viral infections.

We also observed that 13 of 17 patients with COVID-19 had stereotypic variable heavy chain (VH) antibody clonotypes directed against the receptor binding domain (RBD) of SARS-CoV-2 spike protein. These antibody clonotypes were composed of immunoglobulin heavy variable 3-53 (IGHV3-53) or IGHV3-66 and immunoglobulin heavy joining 6 (IGHJ6) genes. These clonotypes included IgM, IgG3, IgG1, IgA1, IgG2, and IgA2 subtypes and had minimal somatic mutations, which suggested swift class switching after SARS-CoV-2 infection. The different IGHV chains were paired with diverse light chains resulting in binding to the RBD of SARS-CoV-2 spike protein. Human antibodies specific for the RBD can neutralize SARS-CoV-2 by inhibiting entry into host cells. We observed that one of these stereotypic neutralizing antibodies could inhibit viral replication in vitro using a clinical isolate of SARS-CoV-2. We also found that these VH clonotypes existed in 6 of 10 healthy individuals, with IgM isotypes predominating.

These findings suggest that stereotypic clonotypes can develop de novo from naïve B cells and not from memory B cells established from prior exposure to similar viruses. The expeditious and stereotypic expansion of these clonotypes may have occurred in patients infected with SARS-CoV-2 because they were already present.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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beyond the pandemic

[SP2-COVID19 and multi-omics study [KNIH Joint Symposium]]

Multi-omics profiling of peripheral immune system in response to SARS-CoV2 infections

Yeonsook Kim[1], Nam-Hyuck Cho[2], Jeong-Seok Lee[3], Dong Hyun Park[4] and Woong-Yang Park[4]

[1]Chungnam National University Hospital, [2]Seoul National University, [3]GENOMEinSIGHT and [4]Geninus Inc., Korea

As a national project led by the Korea Disease Control and Prevention Agency (KDCA), the systemic approaches to collect biological specimens, multi-omics data and clinical information of COVID-19 patients were driven through multi-institutional efforts. To characterize the systemic host response to SARS-CoV2 infection, we will investigate longitudinal samples of 420 patients with biochemical tests, cytokine profiling, single cell RNA sequencing, COVIDseq, whole genome sequencing, HLA-typing. We will present the preliminary results on the multi-omics analysis of COVID-19 patients with mild symptoms.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[Workshop - Shimadzu Scientific Korea Corp.]

차세대 유전자가위 CRISPR PLUS 단백질 개발과 이의 활용

Jiwon Sarah Choi

㈜지플러스생명과학

(주)지플러스 생명과학은 CRISPR 유전자가위기술을 기반으로 혁신 신약을 개발하는 회사입니다. 유전체 편집 효율을 향상시킨 CRISPR PLUS, gfCas12a를 개발하였으며 이를 사용해 암 특이적 DNA를 타겟으로 암세포 선택적으로 사멸을 유도하는 항암신약 Cancerase를 구축하고 있습니다. 현재까지 개발된 유전자 가위 기술과 면역세포치료제, 희귀유전자 치료제 등 적용 가능한 연구 분야를 소개하고자 합니다.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[Workshop - Y-Biologics Inc.]

A renowned biotech company in South Korea for its expertise in antibody science

Young Woo Park

Y-Biologics Inc.

Founded in 2007, Y-Biologics is a biotech company specialized in discovering and developing innovative antibody-based therapeutics for the treatment of cancer. We have secured the pipeline by utilizing two proprietary technologies, a fully human antibody cDNA library and unique T cell bispecific antibody format.

〈Platform Technology〉

- Ymax®-ABL: Proprietary fully human naïve cDNA scFv phage library

- ALiCE(Antibody Like Cell Engager): Novel format of T cell bispecific antibody

〈Pipeline〉

Pipeline with various modalities including monoclonal / bispecific antibody, and ADC in the fields of immunooncology and autoimmune disease

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[Workshop - Geninus Inc.]

Single Cell : Powerful technique for improving our understanding of human health

Siyoung Lee

Geninus Inc.

Until the early 2000s, the time and cost of analyzing a person's genome were astronomical, but in just 10 years, the development of genomic analysis technology and cost reduction led to single-cell research. Single-cell RNA sequencing allows us to identify the expression of various cells that were not identified in traditional Bulk RNA sequencing. Each expression from thousands of different cells enabled the formation of clusters, which enabled the discovery of new biomarkers and new cell types. Single-cell RNA sequencing is applicable beyond simple cell type classification to the development of new drugs through precision medical approaches. Single-cell RNA sequencing technology will evolve gradually, and Genius will deliver the results customers want with a variety of state-of-the-art services and application services.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[Workshop - KRIBB]

LMO safety management and securing biosafety

Sun-Hwa Lee

KRIBB NRSH

Along with the development of biotechnology, various Living modified organisms(LMOs) are being developed. The Cartagena Protocol(biosafety protocol) for LMO safety management was adopted as an annexed Protocol to the Convention on Biological Diversity. The biosafety Protocol aims to prevent risks that may occur to humans and the environment when LMOs transport among nations. South Korea has legislated the LMO Act to implement the biosafety Protocol and has been in effect since 2008. Following the LMO Act, Ministry of science and ICT(MSIT) takes charge of the safety management of LMO for research and development. LMO researcher must abide by the LMO Act and LMO safety management system.

International Conference 2021
LIFE
May 25(Tue) ~ May 27(Thu), 2021
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[YSP-1]

Acetylated alpha tubulin regulates survival of cancer stem cells

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Targeting mitochondrial metabolism (bioenergetics) have emerged as a new promising approach for cancer treatment. Recent studies have shown that cancer stem cells (CSCs) depend on mitochondrial oxidative phosphorylation (OXPHOS) for survival. CSC's metabolism for survival following stress stimuli regulated by cellular cytoskeleton by modulating mitochondrial functional change is unknown. In this study, we showed that acetylated alpha tubulin (ac-AT), acetylation of lysine 40 on alpha tubulin whose expression is enriched in patients with worse prognosis, targets mitochondrial metabolism. We have demonstrated that increased ac-AT regulated by Wnt Pathway provides an advantage to CSCs to survive in stress conditions and to oxidize fatty acid preferentially, an opportunistic energy source. Using human gastric cancer cell lines, stress-resistant cell lines which we established previously, and 3D patient-derived organoids, cell survival and ability of mitochondrial respiration capacity were assessed following acetylation status of alpha tubulin. Total oxygen consumption rate (OCR), mitochondrial complex II-specific OCR, and the preference of energy sources were measured using seahorse analyzer. Subcellular fractionation, confocal immunofluorescence microscopy, immunoprecipitation, PLA assay, crosslinking assay and SDS PAGE after BN PAGE were used to identify localization of ac-AT and interaction between SDHA. We have identified that ac-AT resides in mitochondrial inner membrane and interacts with SDHA, a main subunit of mitochondrial respiratory complex II resulting in enhancement of its enzymatic activity in acetylation dependent manner. Our data demonstrated that mitochondrial functional augmentation regulated by tubulin acetylation can give CSCs to survive in stress conditions. Targeting of ac-AT and electron complex II may merit therapeutic strategy for drug resistant tumor patients.

Keywords: Cancer stem cells, Acetylated alpha tubulin, Mitochondrial bioenergetics

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LIFE
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[YSP-2]

Oncogenic fusion of BCAR4 activates EGFR signaling and is sensitive to dual inhibition of EGFR/HER2

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Metastasis and invasion contribute to the high mortality of cancer patients. We previously reported CD63-BCAR4 fusion as a novel oncogene that significantly enhanced cell migration and metastasis in lung cancer. Fusion transcripts of BCAR4 have been identified in lung cancer patients who did not harbor any known activating mutations of EGFR and KRAS genes. Ectopic expression of CD63-BCAR4 protein in normal bronchial epithelial cells resulted in the enhanced cell proliferation and migration than controls cells. Mouse xenograft model demonstrated in vivo tumorigenicity by CD63-BCAR4 fusion protein. Additionally, metastatic tumors were found in the livers and lungs of the NOG mice injected with CD63-BCAR4 overexpressing BEAS-2B cells. We confirmed a significant downregulation of E-cadherin and an upregulation of N-cadherin and SLUG upon the overexpression of CD63-BCAR4 fusion and suggested the activation of EMT (Epithelial to mesenchymal transition) signals contributed to enhanced migration.

To identify effective inhibitors for the metastatic activity induced by BCAR4 fusion, we have screened a drug library of 381 FDA-approved compounds. The effect of drugs on cell migration was evaluated by monitoring the wound healing areas using the Incucyte Zoom live-cell analysis system. Drugs that decreased cellular mobility of fusion overexpressing cells compared to control cells were selected as candidates. Erlotinib, Canertinib and Lapatinib demonstrated the inhibitory effects on migration as a result of library screening.

Furthermore, ectopic expression of CD63-BCAR4 activates EGFR signaling, even in normal bronchial epithelial cells, as judged by phosphorylation of the tyrosine residue of EGFR protein. We also confirmed increased level of phosphorylation of EGFR protein in the resected tumors from the mice injected with CD63-BCAR4 overexpressing cells.

Tyrosine kinase inhibitors of EGFR family significantly inhibited the migration of BCAR4 fusion overexpressing cells and induced apoptosis at high concentrations. Among the EGFR family TKIs, canertinib, a dual EGFR/HER2 inhibitor showed the best inhibitory effect on cell migration and viability of BCAR4 fusion overexpressing cells. We then examined the effect of canertinib in vivo with mouse xenograft model. Oral administration of canertinib to the xenografted mice reduced tumor growth and liver metastasis induced by CD63-BCAR4 fusion gene. Canertinib treatment also reduced expression of EMT marker as SLUG, N-Cadherin. Taken together, these results suggest EGFR TKIs as the potential therapeutic option for BCAR4 fusion haboring lung cancer patients.

Keywords: Metastasis, BCAR4, Fusion gene, CD63-BCAR4, Lung adenocarcinoma

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[YSP-3]

POLYUNSATURATED FATTY ACID BIOSYNTHESUS PATHWAY DETERMINES FERROPTOSIS SENSITIVITY IN GASTRIC CANCER

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Ferroptosis is an iron-dependent regulated necrosis mediated by lipid peroxidation. Cancer cells survive under metabolic stress conditions by altering lipid metabolism, which may alter their sensitivity to ferroptosis. However, the association between lipid metabolism and ferroptosis is not completely understood. In this study, we found that the expression of elongation of very long-chain fatty acid protein 5 (ELOVL5) and fatty acid desaturase 1 (FADS1) is upregulated in mesenchymal-type gastric cancer cells (GCs), leading to ferroptosis sensitization. In contrast, these enzymes are silenced by DNA methylation in intestinal-type GCs, rendering cells resistant to ferroptosis. Lipid profiling and isotope tracing analyses revealed that intestinal-type GCs are unable to generate arachidonic acid (AA) and adrenic acid (AdA) from linoleic acid. AA supplementation of intestinal-type GCs restores their sensitivity to ferroptosis. Based on these data, the polyunsaturated fatty acid (PUFA) biosynthesis pathway plays an essential role in ferroptosis; thus, this pathway potentially represents a marker for predicting the efficacy of ferroptosis-mediated cancer therapy.

Keywords: Ferroptosis, Lipid Peroxidation, ELOVL5, FADS1

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[YSP-4]

SPATIAL EPITRANSCRIPTOMICS REVEALS A-TO-I EDITOME IN RELATION TO CANCER STEM CELL-LIKE MICRONICHES

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In-depth analysis of tumor microenvironment with spatial context requires tools that enable spatially targeted in-depth analysis of transcriptomes and epitranscriptomes. Here, we introduce Select-seq that isolates the region of interest as small as single cells from the immunofluorescence stained tissue and obtains the full-length transcriptome data. Select-seq produces full-length spatial transcriptome data, with which we analyzed the transcriptomic and epitranscriptomic features including gene expression analysis, alternative splicing variant typing, B cell receptor sequencing, and even adenosine-to-inosine (A-to-I) base editing by adenosine deaminases acting on RNA (ADAR) enzymes, all connected to the staining and spatial information of the tissue. In other words, Select-seq generates a multi-modal data of transcriptome, epitranscriptome, and staining/spatial information. We demonstrated Select-seq on tumor tissue section from triple negative breast cancer patient. To characterize the regions of interests, we immunofluorescently stained a tumor section from triple negative breast cancer tissue sections with CD44 and ALDH1. After categorizing the regions of interests (5 to 10 cells), we isolated the cells and the full-length transcriptome was sequenced therein. Through sequencing the full-length transcriptome with a short read next generation sequencing platform (Illumina), we were able to decipher cancer-stem-cell-like microniches in the section. In the same microniches, we were able to characterize immunosuppression related gene signatures and ferroptosis, a non-apoptotic iron-mediated programmed cell death, related characteristics. Especially we observed non-synonymous A-to-I edited event in one of the peroxidases, implicating possible relationship between the A-to-I editing event and ferroptosis. We were also able to analyze further data from 109 bulk transcriptomes from the cancer genome atlas (TCGA), in which the complex mechanisms behind ferroptosis inhibition might suggest therapeutic options for the TNBC patients with upregulated gene levels associated with ferroptosis.

Keywords: Spatial epitranscriptomics, Spatial transcriptomics, A-to-I editing, Ferroptosis, Triple negative breast cancer

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[YSP-5]

FUNCTIONAL COORDINATION OF BET FAMILY PROTEINS UNDERLIES ALTERED TRANSCRIPTION ASSOCIATED WITH MEMORY IMPAIRMENT IN FRAGILE X SYNDROME

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Bromodomain and extraterminal proteins (BET) are epigenetic readers that play critical roles in gene regulation. Pharmacologic inhibition of the bromodomain present in all BET family members is a promising therapeutic strategy for various diseases, but its impact on individual family members has not been well understood. Using a transcriptional induction paradigm in neurons, we have systematically demonstrated that three major BET family proteins (BRD2/3/4) participated in transcription with different recruitment kinetics, interdependency and sensitivity to a bromodomain inhibitor, JQ1. In a mouse model of Fragile X syndrome (FXS), BRD2/3 and BRD4 showed oppositely altered expression and chromatin binding, correlating with transcriptional dysregulation. Acute inhibition of CBP/p300 histone acetyltransferase (HAT) activity restored the altered binding patterns of BRD2 and BRD4 and rescued memory impairment in FXS. Our study emphasizes the importance of understanding the BET coordination controlled by a balanced action between HATs with different substrate specificity.

Keywords: BET family proteins, Epigenetics, Enhancers, Neurons, Fragile X Syndrome.

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[YSP-6]

CONTROL OF NEUROGENIC COMPETENCE IN MAMMALIAN HYPOTHALAMIC TANYCYTES

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Hypothalamic tanycytes, radial glial cells that share many features with neuronal progenitors, can generate small numbers of neurons in the postnatal hypothalamus, but the identity of these neurons and the molecular mechanisms that control tanycyte-derived neurogenesis are unknown.

In this study, we show that tanycyte-specific disruption of the Nuclear factor I (NFI) family of transcription factors (Nfia/b/x) robustly stimulates tanycyte proliferation and tanycyte-derived neurogenesis. Single-cell RNA- and ATAC-Seq analysis reveals that NFI factors repress Shh and Wnt signaling in tanycytes, and modulation of these pathways blocks proliferation and tanycytederived neurogenesis in Nfia/b/x-deficient mice. Nfia/b/x-deficient tanycytes give rise to multiple mediobasal hypothalamic neuronal subtypes that can mature, fire action potentials, receive synaptic inputs, and selectively respond to changes in internal states. These findings identify molecular mechanisms that control tanycyte-derived neurogenesis, which can potentially be targeted to selectively remodel the hypothalamic neural circuitry that controls homeostatic physiological processes.

Keywords: Tanycytes, adult neurogenesis, Hypothalamus,single-cell RNA sequencing, Nuclear factor I.

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[YSP-7]

Astrocytes phagocytose adult hippocampal synapses for circuit homeostasis

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Adult synapses constantly undergo synaptic turnover during experience-dependent plasticity and cognitive functions. However, it is unclear how synapses in the adult brain are eliminated and whether synapse elimination has a direct role in circuit homeostasis. Astrocytes eliminate synapses by phagocytosis during postnatal development. By phagocytosing synapses through the MEGF10 and MERTK phagocytic receptors, astrocytes actively contribute to activity-dependent synapse pruning and developmental refinement of circuits. Moreover, contrary to the previous notion that microglia are the sole mediators of synapse elimination, astrocytes have been shown to have a major role in eliminating synapses in developing brains. On the basis of these findings, we hypothesized that synapses in the adult brains are also refined by astrocytic phagocytosis, and that such elimination is critical for maintaining circuit homeostasis. Here we show that astrocytic phagocytosis is important for maintaining proper hippocampal synaptic connectivity and plasticity. By developing and using mCherry-eGFP phagocytosis reporters, we find that excitatory and inhibitory synapses are eliminated by glial phagocytosis in the CA1 region of the adult mouse hippocampus. Unexpectedly, we found that astrocytes have a major role in the neuronal activity-dependent elimination of excitatory synapses in the hippocampus. Furthermore, mice in which astrocytes lack the phagocytic receptor MEGF10 show a reduction in the elimination of excitatory synapses; as a result, excessive but functionally impaired synapses accumulate. Finally, Megf10-knockout mice show defective long-term synaptic plasticity and impaired formation of hippocampal memories. Together, our data provide strong evidence that, for the first time, astrocytes, but not microglia, constantly eliminate excessive and unnecessary multiple excitatory pre- and post-synaptic connections via MEGF10 in the adult hippocampus, and without this astrocytic function, precise re-patterning and homeostasis of hippocampal circuit connectivity cannot be maintained. These findings would have profound implications for our understanding of many neurobiological processes, including synaptic plasticity, learning and memory, synaptic homeostasis and neurological disorders.

Keywords: Astrocyte, Synapse, Phagocytosis, learning and memory, multiple synaptic connection

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[YSP-8]

CYTOSOLIC CALCIUM REGULATES TDP-43 LOCALIZATION THROUGH CALPAIN-A AND IMPORTIN α3

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TDP-43 is a nuclear protein that mislocalizes to the cytoplasm in ~97% of amyotrophic lateral sclerosis (ALS) patients. Nucleocytoplasmic transport (NCT) defect and TDP-43 cytoplasmic inclusion that sequesters and depletes nuclear TDP-43 have been shown to contribute to the cytoplasmic mislocalization of TDP-43. However, which cellular factors control the activity of NCT thereby affecting TDP-43 mislocalization is less known. Here, we used fluorescence recovery after photobleaching and optogenetics to identify cytosolic calcium as a key cellular factor upstream of NCT of TDP-43. First, we observed a dynamic and reversible changes in TDP-43 localization in Drosophila sensory neurons during development. These changes were regulated by cytosolic calcium level. Second, we screened for calcium-dependent regulator proteins and nuclear transport receptors that can modulate NCT of TDP-43 and identified Calpain-A and Importin α3 as the main players. Finally, upregulating the cytosolic calcium-Calpain-A-Importin α3 pathway in a C9orf72 ALS fly model reduced cytoplasmic mislocalization of TDP-43 and mitigated behavioral defects. Our study proposes the calcium-Calpain-A-Importin α3 pathway as a potential therapeutic target of ALS.

Keywords: nucleocytoplasmic transport, Drosophila melanogaster, amyotrophic lateral sclerosis, calcium, TDP-43

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[YSP-9]

HIERARCHICAL REGULATION OF AUTOPHAGY DURING ADIPOCYTE DIFFERENTIATION

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We previously showed that some adipogenic transcription factors such as CEBPB and PPARG directly and indirectly regulate autophagy gene expression in adipogenesis. The order and the effect of these events are undetermined. In this study, we modeled the gene expression, DNA-binding of transcriptional regulators, and histone modifications during adipocyte differentiation and evaluated the effect of the regulators on gene expression in terms of direction and magnitude. Then, we identified the overlap of the transcription factors and co-factors binding sites and targets. Finally, we built a chromatin states model based on the histone marks and studied their relation with the factors' binding. Adipogenic factors differentially regulated autophagy genes as part of the differentiation program. Co-regulators associated with specific transcription factors and preceded them to the regulatory regions. Transcription factors differed in the binding time and location, and their effect on expression was either localized or long-lasting. Adipogenic factors disproportionately targeted genes coding for autophagy-specific transcription factors. To sum, a hierarchical arrangement between adipogenic transcription factors and co-factors drives the regulation of autophagy during adipocyte differentiation.

Keywords: transcription-factors, autophagy, differentiation, adipocyte, hierarchical-regulation

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[YSP-10]

GE11-expressing bovine milk-derived extracellular vesicles for EGFR targeted delivery of oxaliplatin to colorectal cancer

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Anticancer drugs, such as oxaliplatin are commonly used to treat colorectal cancer. However, owing to their low response rate and adverse effects, the development of efficient drug delivery systems is required. Bovine milk derived extracellular vesicles (milk EV) can be potential drug delivery systems since they can be obtained with a large amount and are known to be safe after system administration. However, studies for surface modification of milk EV are limited. Milk EV were isolated by using differential centrifugation and ultracentrifugation. To display GE11 peptide onto the surface of milk EV, the cholesterol-PEG-DBCO was incorporated into the membrane of milk EV. Then, azide-modified GE11 peptides were treated to the DBCOmodified milk EV. The GE11-expressing milk EV (GE11-milk EV) were loaded with oxaliplatin using simple incubation. GE11-milk EV showed superior drug delivery efficiency to EGFR overexpressing colorectal cancer cells and breast cancer cells compared to bare milk EV. In the colorectal cancer xenograft mouse model, intravenous administration of oxaliplatin-loaded GE11-milk EV resulted in greater inhibition of tumor growth as compared to the treatment of equivalent amount of free oxaliplatin. The oxaliplatin-loaded GE11-milk EVs have the potential to replace existing anticancer drugs, such as 5-FU, oxaliplatin.

Keywords: Milk, Extracellular vesicles, Drug delivery systems, Colorectal cancer, EGFR targeting

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[YSP-11]

MACROPHAGE-PREFERABLE DELIVERY OF THE NLRX1 PROTEIN AMELIORATES LETHAL SEPSIS BY REGULATING NF-κB AND INFLAMMASOME SIGNALING ACTIVATION

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Sepsis is an acute systemic inflammatory disease triggered by bacterial infection leading organ dysfunctions that macrophages are responsible for major triggering of hyper-inflammation. Treatment options are limited to antibiotics and drugs to manage the symptoms of sepsis, but there are currently no molecular-targeted drugs. Here, we identified a novel macrophage-preferable delivery peptide, C10, which we conjugated to truncated domains of NLRX1 (leucine-rich repeat region (LRR), and nucleotide binding domain (NBD)) to obtain C10-LRR and C10-NBD. Leucine rich amino acid of C10 enables macrophage preferable moieties that efficiently deliver a cargo protein into macrophages in vitro and in vivo. C10-LRR but not C10-NBD significantly improved survival in an LPS-mediated lethal sepsis model. C10-LRR efficiently negatively regulated IL-6 production in peritoneal macrophages via prevention of IκB degradation and p65 phosphorylation. In addition, C10-LRR negatively regulated IL-1β production by preventing caspase-1 activation with a sustained mitochondrial MAVS level. Finally, co-treatment with anti-TNFα antibody and C10-LRR had a synergistic effect in a sepsis model. Collectively, these findings indicate that C10-LRR could be an effective therapeutic agent to treat systemic inflammation in sepsis by regulating activation of both NF-κB and inflammasome signaling.

Keywords: Sepsis, NLRX1, Cell penetrating peptide, Macrophage, NF-κB, Inflammasome

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[YSP-12]

Cinnamomum verum-derived O-Methoxycinnamaldehyde is an anti-inflammatory novel Tlymphocyte NFAT regulator with therapeutic potential in the context of depressive disorder

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Homeostasis requires balanced co-operation between the nervous, immune, and endocrine systems. Inflammation is implicated in depressive disorder pathophysiology, including via cytokine-altered nervous system functions. On T-cell activation, inflammatory stimuli activates transcription factor NFAT to induce expression of itself and of depression marker cytokines TNFα and IL-2. Existing NFAT inhibitors such as cyclosporin A target nuclear translocation and exhibit unfavorable adverse effect profiles. Inhibition of alternate aspects of NFAT function is therefore desirable. Because in vitro and animal model studies support the anti-inflammatory and antidepressant effects of Cinnamomum verum (CV), the present study evaluated its impact on depression-like behavior in a murine model of inflammationinduced depression, including elucidating underlying molecular mechanisms. Pre-treatment with CV extract or constituent O-Methoxycinnamaldehyde (MCA) dose-dependently ameliorated both inflammation-induced depressionlike behavior and increases in plasma TNFα and IL-2 levels. Non-cytotoxic levels of CV extract or MCA concentration-dependently ameliorated activation-induced increases in T-cell TNFα and IL-2 mRNA levels in vitro (accompanied by MCA-mediated decreases in TNFα and IL-2 protein secretion). Finally, CV extract or MCA ameliorated activation-induced increases in NFAT (but not NF-κB p65) mRNA and protein levels, but did not inhibit NFAT nuclear transcription. Instead, MCA p38 MAPK-independently decreased NFAT mRNA levels by promoting NFAT mRNA decay. Post-transcriptional regulation of T-cell NFAT is a novel anti-inflammatory mechanism of MCA. Overall, findings suggest that the CV extract-mediated decrease in inflammation and inflammation-induced depression-like behavior may be attributable to this MCA mechanism. Pending validation of this hypothesis and comprehensive safety and efficacy evaluation, MCA may represent an alternative or adjuvant to existing NFATtargeting immunosuppressants for clinical prophylaxis or therapy in the context of inflammation-induced depressive disorder or other T-cell-associated inflammatory disorders.

Keywords: O-Methoxycinnamaldehyde, Cinnamomum verum, inflammatory depression, NFAT, IL2, TNFα

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[YSP-13]

Fundamental principles of SMC-protein-mediated chromosome organization

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In a eukaryotic cell, 2 meter DNA is compacted into a micro-meter sized chromosome, but the mechanism by which the extremely long and negatively charged polymer is compacted into this tiny structure remain elusive. Recent evidence suggested that Structural Maintenance of Chromosome (SMC) protein complexes such as cohesin and condensin are the key organizers of the spatiotemporal structure of chromosomes by extruding DNA loops1-3. However, the molecular mechanism how such SMC motor proteins extrude DNA loop remained completely unknown. In our work using liquid- phase High-Speed Atomic Force Microscopy (HS AFM) and magnetic tweezers (MT)4,5, we obtained experimental data for yeast condensin acting on individual DNA molecules. The findings suggest a scrunching model in which the SMC complex extrudes a DNA loop by a cyclic switching of its conformation between open and collapsed shapes. In addition, we show that the yeast cohesin complex unexpectedly can exhibit a new type of phase separation6 by locally bridging the DNA. Our findings suggest that both DNA loop extrusion and phase separation by SMC complexes are fundamental building blocks of chromosome organization.

Keywords: DNA loop extrusion, Phase separation, HS AFM, Magnetic tweezers

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[YSP-14]

STRUCTURAL ANALYSIS OF THE MOLECULAR INTERACTION BETWEEN AIMP2-DX2 AND HSP70 ON THE CANCER DEVELOPMENT

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Aminoacyl-tRNA synthetase-interacting multifunctional protein 2 (AIMP2), which is a crucial component for a Multi-synthetase complex (MSC), is well known to separates from the complex and acts as a potent tumor suppressor. Recently, it was revealed that an exon 2 deleted splicing variant of AIMP2 (AIMP2-DX2) is often upregulated in diverse cancers, and 70kda heat-shock protein (HSP70) is critical to determine the cellular level of AIMP2-DX2. Although the biological implication of the interaction between AIMP2-DX2 and HSP70 has been suggested, the structural aspect of the interaction remains elusive. Here, we studied structural details of the interaction between AIMP2-DX2 and HSP70 by using X-ray crystallography and NMR spectroscopy. It was found that both N-terminal flexible region and GST domain of AIMP2-DX2 are involved in the interaction with the substrate-binding domain of HSP70, which results in the stabilization of AIMP2-DX2 by preventing the AIMP2-DX2 from Siah1-dependent ubiquitination and progression to tumorigenesis. It was confirmed that inhibiting the interaction between the AIMP2-DX2 and HSP70 by chemical compound, BC-DXI-495, suppressed cancer cell growth. Structural modeling in which BC-DXI-495 is docked into the hydrophobic pocket of AIMP2-DX2 was performed and this hydrophobic pocket is close to the HSP70-binding surface, suggesting an inhibitory effect of BC-DXI-495 on HSP70-AIMP2-DX2 binding. These results will provide crucial structural information to elucidate the molecular mechanism of oncogenic activity of DX2 on cancer development.

Keywords: AIMP2-DX2, HSP70, protein structure, protein-protein interaction, cancer development

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[YSP-15]

ADIPOCYTE HIPPO SIGNALING COORDINATES ADIPOSE TISSUE HOMEOSTASIS AND SYSTEMIC METABOLISM BY REGULATING ADIPOCYTE DEDIFFERENTIATION AND LEPTIN

Sungwoo CHOI[1,2], Thi Hai Yen TRAN[3,4], Ju-Gyeong KANG[1,3], Kun-young PARK[2], Myungsun PARK[2], Hyemi SHIN[2], Sunhye JEONG[3,5], David EISENBARTH[3], Jinhyuk CHOI[2], Jongeun PARK[2], Jae Myung SUH[1,2*], Daesik LIM[3*]

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Adipose tissue is a metabolic and endocrine organ that regulates whole-body energy balance. Hippo signaling is known to regulate tissue size and tissue-specific function, however, the role in adipocyte is not fully understood yet. Here we show that adipocyte YAP/TAZ activation by loss of LATS1/2 deletion leads to smaller adipocyte and subsequent reprogramming into progenitor-like cells, which is attributed to elevated serum leptin level compared to its decreased fat mass. We found YAP/TAZ directly upregulates leptin gene transcription and uncouples between adipose tissue mass and serum leptin level. Our results demonstrate how adipocyte coordinates leptin secretion together with adipose tissue size control. Collectively, we suggest adipocyte hippo signaling regulates adipose tissue homeostasis and systemic metabolism by manipulating adipocyte plasticity and leptin level

Keywords: Adipocyte Dedifferentiation, Adipocyte Plasticity, Leptin, Lipodystrop