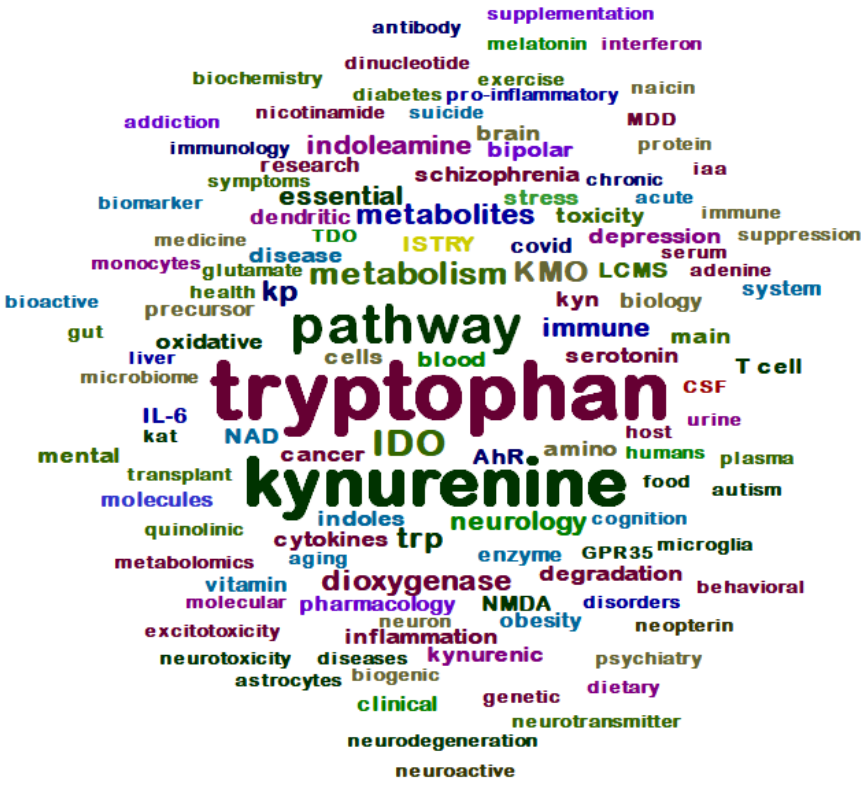
*I*NTERNATIONAL *S*OCIETY FOR *TRY*PTOPHAN RESEARCH



ISTRY ONLINE WEBINAR

ISTRY 7TH ONLINE WEBINAR AGENDA
14 MAY 2025 (Japan Standard Time)

Introduction

From 15.45 Virtual Reception by Host – Zoom login

16:00 - 16:10 Welcome and Opening remarks by ISTRY President, Prof Stefano COMAI

Senior Guest Speakers

16:10 - 16:35 **Dysregulation of serum tryptophan metabolism in patient with COVID-19**

Prof. Hidetsugu FUJIGAKI
Fujita Health University, Japan

Chaired by Prof. Tsutomu Fukuwatari (ISTRY Executive Committee)

16:35 - 16:40 Q & A Session

16:40 - 17:05 **Despair, Depression, and Dysregulated Dissonance: Decoding Tryptophan Trajectories in KAT2$^{-/-}$ Mice**

Dr. Masaru TANAKA
University of Szeged, Hungary

Chaired by A/Prof. Yuki Murakami (Kansai Medical University)

17:05 - 17:10 Q & A Session

NAD Research in Focus

17:10 - 17:23 **Role of gut microbiota in the metabolic fate of NAD+ precursors**

Asst. Prof. Keisuke YAKU
University of Toyama, Japan

Chaired by A/Prof. Alato Okuno (Shibata Gakuen University)

17:23 - 17:25 Q & A Session

17:25 - 17:48 **Changes in pancreatic tryptophan and NAD metabolism-related gene expression in non-alcoholic fatty pancreatic disease (NAFPD)**

MSc. Mika KITTAKA
Notre Dame Seishin University, Japan

Chaired by A/Prof. Alato Okuno (Shibata Gakuen University)

17:48 - 17:50 Q & A Session

Closing

17:50 - 18:00 Acknowledgment and closing remark by ISTRY President

Dysregulation of serum tryptophan metabolism in patient with COVID-19

Hidetsugu FUJIGAKI, *Ph.D*
Professor

Department of Advanced Diagnostic Development Fujita Health University, Aichi, JAPAN

Abstract:
Tryptophan (Trp) is an essential amino acid which is metabolized along the kynurenine, serotonin, and indole pathways. An imbalance of Trp metabolism in biological samples has been reported in several diseases including inflammatory diseases, neuropsychiatric diseases, and cancer. In this study, we developed a simultaneously quantitative method for Trp metabolites by LCMS, and serum samples from patients with COVID-19 were analyzed. Trp metabolites elevated in patients with COVID-19 were kynurenine (Kyn), 3-hydroxykynurenine, anthranilic acid, and quinolinic acid. Kyn was markedly elevated in the sera collected within 10 days after the onset of symptoms from severe patients. Trp metabolites decreased in patients with COVID-19 were Trp, serotonin (5-HT), indole-3-acetic acid, indole-3-butyric acid, 3-hydroxyanthranilic acid, and xanthurenic acid. Among them, 5-HT was markedly decreased in the sera collected within 10 days after the onset of symptoms from severe patients. This study demonstrated that Trp metabolism was altered in patients with COVID-19. Elevated Kyn pathway metabolites and decreased 5-HT in severe patients may be related to hyper-inflammation and abnormal coagulation/fibrinolysis system.

Despair, Depression, and Dysregulated Dissonance: Decoding Tryptophan Trajectories in kat2-/- Mice

Masaru TANAKA, *Ph.D.*
Senior Research Fellow

HUN-REN-SZTE Neuroscience Research Group, Hungarian Research Network
University of Szeged, HUNGARY

Abstract:
Despair, depression, and biochemical dissonance converge on the tryptophan–kynurenine metabolism, yet how emotional stress steers tryptophan metabolites remains uncertain. Kynurenine aminotransferase II (KAT II) converts kynurenine to neuroprotective kynurenic acid; its absence may push the metabolic pathway toward neurotoxicity. We generated CRISPR/Cas9 kat2−/− mice and compared 8-week males with wild types across emotional, cognitive, motor, and metabolomic domains. Behavioral batteries spanned despair, anxiety, memory, and locomotion assays, paired with ultra-high-performance LC-MS/MS of plasma and urine metabolites, enzyme activities, and oxidative and excitotoxic indices. kat2−/− mice displayed pronounced despair-like behavior without excess anxiety, alongside hypoactivity and blunted exploration. Metabolomics revealed >90 % losses of kynurenic, xanthurenic, and anthranilic acids, a three-fold rise in 3-hydroxykynurenine, heightened kynurenine-3-monooxygenase activity, and oxidative-stress and NMDA agonist/antagonist ratios that soared ten-fold; serotonin catabolite 5-hydroxyindoleacetic acid and gut-derived indole-3-acetic acid concurrently fell. This webinar demonstrates that deleting KAT II diverts tryptophan metabolism toward pro-oxidative, excitotoxic dissonance, precipitating despair-induced

depression and motor deficits, and yields a double-hit model decoding metabolite trajectories linking stress to neurodegeneration. By spotlighting urinary metabolites as non-invasive biomarkers and exposing enzyme nodes ripe for intervention, the findings energize translational strategies aimed at harmonizing dysregulated dissonance across brain, body, and microbiome.

Role of gut microbiota in the metabolic fate of NAD+ precursors

Keisuke YAKU, *Ph.D.*
Assistant Professor

Dept. of Molecular and Medical Pharmacology
University of Toyama, JAPAN

Abstract:
Nicotinamide adenine dinucleotide (NAD^+) is an essential metabolite derived from tryptophan, involved in energy production, DNA repair, and protein post-translational modification. Age-associated decline in NAD^+ levels has been linked to physiological deterioration, prompting extensive research into NAD^+ restoration strategies. Oral administration of NAD^+ precursors is a simple and effective approach; consequently, the role of gut microbiota in NAD^+ metabolism has attracted growing interest. In this study, we investigated the involvement of gut microbiota in the metabolic fate of NAD^+ precursors—specifically nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN)—which are widely used in human clinical trials.

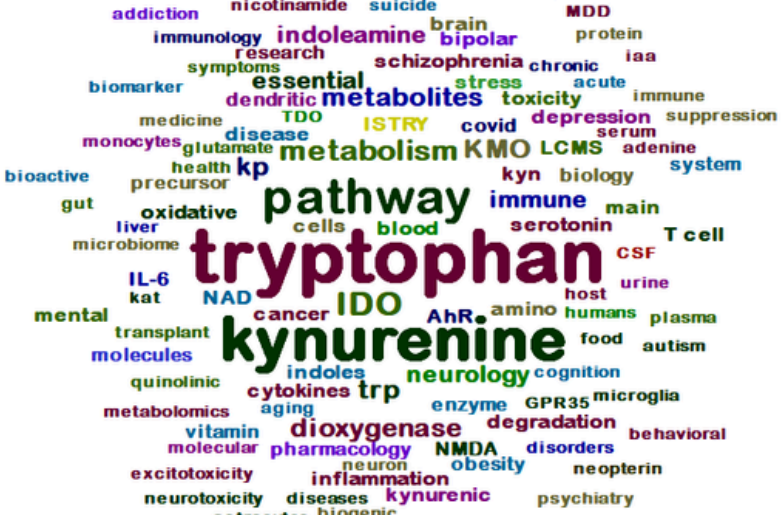
Changes in pancreatic tryptophan and NAD metabolism-related gene expression in non-alcoholic fatty pancreatic disease (NAFPD)

Mika KITTAKA, *M.Sc.*
Ph.D. Student

Division of Comprehensive Human Life Sciences
Notre Dame Seishin University, Okayama, JAPAN

Abstract:
Recently, as the number of pancreatic cancer patients increases, attention has focused on non-alcoholic fatty pancreatic disease (NAFPD). NAFPD, like nonalcoholic fatty liver disease (NAFLD), is caused by obesity, which leads to organ fibrosis and eventually cancer. However, NAFPD and NAFLD share many disparities in the mode of ectopic fat infiltration and pathogenesis mechanisms, making NAFPD a disease that remains an enigma. Tryptophan is an essential amino acid, mostly involved in the biosynthesis of nicotinamide adenine dinucleotide (NAD), a major redox cofactor that plays an important role in various aspects of metabolism, inflammation and ageing, via the kynurenine pathway. In addition to the kynurenine pathway, NAD is also biosynthesised by the Preiss-Handler pathway using

nicotinic acid and the salvage pathway using nicotinamide (NAM). However, the relationship between obesity and NAD metabolism remains unclear. We have previously found that the liver of Gubra Amylin NASH (GAN) feed-induced obese mice not only shows the pathology of NAFLD, but also that gene expression of enzymes in the NAD metabolic pathway is reduced across the board. However, the effect of GAN feed-induced obesity on enzyme gene expression levels of NAD metabolic pathways in the pancreas is unknown. We therefore created a GAN feed-induced NAFLD model mice (GAN-14) in which 7-week-old male C57BL/6J mice were fed a GAN diet for 14 weeks to investigate its effects on pancreatic tissue. The results showed that the gene expression level of the Col1a1 was significantly increased, and a positive Sirius Red staining image was also observed in the pancreas of GAN-14. Based on the above, it was concluded that pancreatic fibrosis occurred in GAN-14. Biochemical analysis of serum also showed that serum amylase levels were significantly increased in GAN-14, indicating that the pancreas was in an inflammatory state. On the other hand, quantitative PCR in the pancreas showed that the gene expression of fibrosis- and inflammation-related factors, enzymes of the kynurenine pathway and NAD metabolism pathway were increased across the board in the GAN-14. In this study, the GAN diet induced obesity model mice not only showed the pathogenesis of NAFLD, but also NAFPD, indicating that the GAN diet can be used to create NAFPD model mice. Interestingly, pancreatic kynurenine and NAD metabolism were increased across the board in NAFPD. The present results may be the first example to demonstrate that GAN diets produce not only NAFLD but also NAFPD. We also found that the variation in NAD metabolism differed between the liver and the pancreas, and concluded that it was related to the respective pathogenesis of NAFLD and NAFPD.



SPEAKERS

Associate Professor Hidetsugu Fugigaki

Dysregulation of serum tryptophan metabolism in patient with COVID-19.

Professor Hidetsugu Fujigaki from Fujita Health University will discuss the role of tryptophan metabolism in patient with COVID-19

Dr. Masaru Tanaka

Despair, Depression, and Dysregulated Dissonance: Decoding Tryptophan Trajectories in kat2 $^{-/-}$ Mice

Dr. Masaru Tanaka from University of Szeged will talk about the use of KAT2 knockout model in studying neuropsychiatric conditions

Assistant Professor Keisuke Yaku

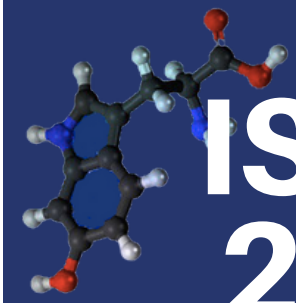
Role of gut microbiota in the metabolic fate of NAD+ precursors

Assistant Professor Keisuke Yaku from University of Toyama will present his work about how gut microbiota impact on NAD metabolism.

Ms. Mika Kittaka

Changes in pancreatic tryptophan and NAD metabolism-related gene expression in non-alcoholic fatty pancreatic disease (NAFPD)

Ms. Mika Kittaka, a PhD student in Notre Dame Seishin University will be presenting her work about tryptophan and NAD metabolism in NAFPD.



ISTRY 2025 Online Webinar

14TH MAY 2025
16:00 - 18:00 (JST)
9:00 - 11:00 (CEST)

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