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ISTRY NEWSLETTER

International Society for Tryptophan Research

INTRODUCTION

A warm welcome to our third issue of the ISTRY newsletter! Six months since our last issue have flown by, and in the scientific community, we are seeing more in-person meetings happening as travel restrictions start to lift around the world. As far as the ISTRY meeting is concerned, the ISTRY executive committee is currently discussing the potential for an in-person meeting. Hopefully, we have some good news to announce in the next Newsletter issue.

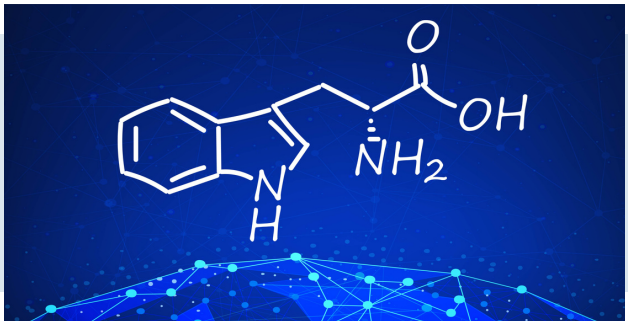
In this issue, we will provide some recent updates on activities organised by ISTRY, followed by a themed topic for this issue on 'Ageing and tryptophan metabolism' and lastly, the very sad news of the passing of Professor Carlo Costa. Indeed, a great loss to the tryptophan research community and we pay our tribute with an obituary of Prof Costa to recollect some of his significant contributions to the tryptophan field.

RECENT UPDATES OF ISTRY ACTIVITIES

Since our last issue, we had our second webinar in April 2022 featuring 3 keynote speakers including our latest Musajo Memorial medallist, Professor Flavio Moroni. Thanks to our supporting audience from the tryptophan research community, we have a similar turnout as the first webinar covering topics on musculoskeletal disorders by Prof Gustavo Duque (Australia), maternal inflammation and neurodevelopmental disorders by Dr. Yuki Murakami (Japan), and lastly, a talk that was 40-years in the making about neuroactive kynurenine metabolites in age-related brain disorders by Prof Flavio Moroni. This has also inspired us with this issue's theme topic on the kynurenine pathway and ageing. The ISTRY executive committee would like to thank all speakers for their participation and contribution to the field. In a month, we will have our third webinar, this time with the theme of Cancer with three wonderful speakers lined up. Stay tuned and **register** your interest.

To date, the ISTRY media team has put together 17 feature articles, 90 tweets, 3 newsletters, and 3 webinars. Coordinated amongst a team of 4, reaching out to over 780 individuals identified as active researchers in the TRP field. On average, our site has an average of over 600 visits per week. We are currently seeking to recruit more members to the media team to provide more frequent outreach and bring the TRP community closer together. This will also pave the way for our next major project that will focus on building capacity in the next generation of early career researchers to ensure the continuity and sustainability of the tryptophan research field. In fact, a recent article in Nature highlighted the current 'brain drain' in the academic sector where early career researchers and skilled postdoctoral fellows are leaving in droves to pursue more lucrative and stable career opportunities in industry. There is an urgent need for leaders in the academic sector to play a bigger role in mentoring early career researchers and postdocs, rather than taking them for granted, otherwise we risk losing the next generation of scientists and jeopardising the hard work of our predecessors. This is precisely the reason for societies and organisations like ours to support and build capacity in young researchers.

WHAT'S INSIDE THIS ISSUE:



AGEING AND THE KYNURENINE PATHWAY

One of the major areas of focus for tryptophan (TRP) metabolism research is its alterations in neurodegeneration. Our current and previous Musajo Medalists have contributed significantly to this field. Hence, the ISTRY media team thought that the theme of 'ageing and the kynurenine pathway' would be of interest to the TRP research community. Ageing is associated with a decline in biological functions and causes cellular distress that results in dramatic metabolic changes. Additionally, it is well known that the natural ageing process is associated with increased inflammation, termed 'inflammaging,' that can consequently alter kynurenine pathway (KP) activity. In this newsletter, we will focus on TRP metabolism and how these metabolites are altered in ageing, potentially driving age-associated disease progression.

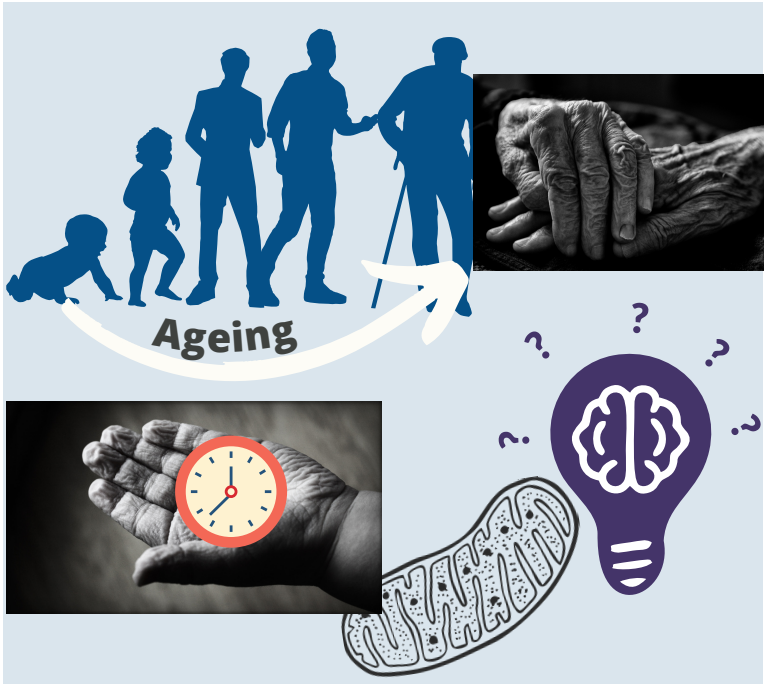
Although age-associated alteration in TRP metabolism is yet to be fully understood, we do know that enhanced TRP metabolic activity does not apply to all downstream KP metabolites in an all-or-none fashion. For example, the shift towards KP activity reduces serotonin bioavailability in the geriatric population. This aligns with age-associated chronic inflammation (i.e., 'inflammaging' – more on this later) leading to increased IDO-1 activity. Data modelling that adjusts for age as a confounding factor suggests that quinolinic acid (QUIN) increases with age, while the opposite is true for kynurenic acid (KYN). Interestingly, lower KYN/TRP ratios are associated with longer lifespans in mammals (S. Ma et al., 2015).

Perhaps one of the most well-known ageing-associated metabolites of TRP metabolism via the KP is nicotinamide adenine dinucleotide (NAD+), which governs cellular bioenergetic activities. Changes to KP pathway activity can affect the overall NAD+ bioavailability evident in many age-related diseases, and also congenital malformations in individuals with defective HAAO and KYNU genes. Furthermore, KP metabolites, specifically 3-hydroxykynurenine (3-HK) and QUIN, can lead to decreased cellular ATP production. In addition to reduced NAD+, some KP metabolites such as 3-hydroxykynurenine and QUIN are known to potentiate oxidative stress that drives mitochondrial damage, thereby contributing to the mitochondrial dysfunction associated with ageing. Taken together, alterations in KYN metabolite production can have profound effects on cellular energy availability, oxidative stress, and mitochondrial health, potentially driving age-related disease pathogenesis.

Age-associated diseases related to KP metabolite alterations

1. Cognitive decline and neurodegenerative diseases

It is inseparable not to mention neurodegenerative disease in relation to cognitive decline and dementia on the topic of ageing, given that age is the biggest risk factor for dementia. The usual TRP metabolism dysfunctional suspects are involved: increased KYN/TRP ratio, QUIN, and decreased KYNA (A. Almulla et al., 2022). We had covered a few feature articles that provide evidence of KP alteration and neurodegeneration in MCI/AD (see 2022 June highlight), and most recently in individuals with long COVID (see 2022 August highlight). Some recent emerging



targets in neurodegeneration are 3-hydroxyanthranilic acid (3HAA) and anthranilic acid (AA). For example, the Framingham study followed 2,067 dementia-free Framingham Offspring Cohort participants to examine their associations with future dementia and AD risk. They found that increased plasma AA levels were associated with a greater risk of dementia. Interestingly, the Australian Imaging, Biomarker and Lifestyle Study of Aging (AIBL), showed that KP alteration precedes progression of dementia, and an increased 3HAA/AA ratio (reflective of higher 3HAA at baseline) predicts progression to dementia. The same study also showed reduced picolinic acid (PIC) in those who progressed to dementia. PIC, being a neuroprotective metabolite in the context of neurodegeneration may exert a widespread effect in ageing considering its role in frailty (see below) and suicide, both of which are prevalent in the geriatric population. Targeting KP metabolism may offer protection against disease progression in addition to being used as a biomarker for neurodegenerative diseases. However, it is important to consider that KP metabolites can confound with age when designing studies in ageing populations.

2. Frailty

If you attended our last webinar in April, you would have heard our first keynote speaker, Prof Gustavo Duque, discussing the role of KP in osteoporosis and sarcopenia associated with the risk of fractures and falls, respectively, that are attributed to frailty (check out the video here). Some important aspects of TRP metabolism in bone biology include the origin of serotonin (i.e., brain vs. gut) which may affect the rate of bone formation and resorption thereby impacting bone integrity; preliminary findings suggest that several KP metabolites including KYN, KYNA, PIC, and QUIN are associated with the degree of frailty (A. Al Saedi et al., 2022). PIC may be a therapeutic target for osteoporosis and sarcopenia by promoting healthy bone cells and muscle development.

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AGEING AND THE KYNURENINE PATHWAY CONTINUED

3. Immunosenescence and inflammaging

The IDO-AhR axis plays a vital role in immune tolerance that has drawn huge attention in the cancer immunology field (check out our upcoming webinar focusing on this topic). In the context of inflammaging, the IDO-AhR axis can promote IL-6, creating a vicious cycle of pro-inflammatory signalling and sustained KP activity that can impact autophagy and senescence processes (F. Sorgdrager et al., 2019). One detrimental impact of sustained KP activity, apart from reduced serotonin production, is the increased QUIN rendering susceptibility to increased risk of mental ill-health, such as depression and suicidality, which are highly prevalent in the ageing population. Another important factor to consider is the association between inflammaging and gut microbiota. Microbial-derived indoles play a role in modulating the immune response and may protect from some diseases. Changes in microbe diversity can result in alterations in microbial-derived TRP metabolites impacting the host immune response, inflammatory state, and TRP availability.

Ageing is a broad topic and what we discussed here is only the tip of the iceberg. It is not hard to pinpoint tryptophan metabolism as one of the key metabolic pathways of interest in ageing, given that KP alteration has been implicated in many age-related diseases such as cardiovascular disease, diabetes, and cancer. We hope that this newsletter commentary has provided a brief insight, into the 'old' and new emerging targets involving the KP in ageing and age-related diseases for treatment and biomarker discovery. Further, lifestyle risk factors, such as diet and physical activity, may alter KP metabolism levels and should be taken into consideration when examining age-related changes.

PROFESSOR CARLO VIRGILIO LUIGI COSTA (1940 - 2022)

It is with great sadness that we are writing of the passing of a longstanding and eminent researcher in the tryptophan field, Professor Carlo Virgilio Luigi Costa, who passed away on the night of August 21, at the age of 82. Prof. Costa was a well-known academic at the University of Padova, Italy, who taught for many years at the Department of Pharmaceutical Sciences, now the Department of Pharmaceutical and Pharmacological Sciences. Before his academic career, Carlo was a member of the dynasty of the Costa barons, one of the oldest families of entrepreneurs from Genova, Italy, and specialised in the trading of flour, wheat, and oil. This business was started in the mid-nineteenth century by Giacomo Costa, who exported the famous Dante Oil to the United States.

However, Carlo's predilection was not to continue the family entrepreneurial tradition. After graduating from the Heidelberg Classical High School in Germany, he decided to devote his life to scientific research. He graduated in Padua and became a Professor at the University of Padua after being a mentee of Prof. Luigi Musajo, a pioneer in tryptophan research and a founder of ISTRY (formerly known as International Study Group for Tryptophan Research). In 1973, Prof. Costa, together with Prof. Musajo and the coworkers from the University of Padova, Prof. Graziella Allegri and Prof. Antonio De Antoni, were the organisers of the 1st ISTRY meeting held in Padova in 1974. Prof. Costa was also among the organisers of the 8th ISTRY Meeting (1995) and the 10th ISTRY Meeting (2002) both held in Padova.

Prof. Costa together with the collaborators of the Tryptophan group at the University of Padova have published more than 150 papers on the metabolism of tryptophan in physiological and pathological conditions. In his academic career, he collaborated with many renowned scientists in the field of tryptophan from around the world. He retired from academia in 2010.

Prof. Costa was a true gentleman at heart, always available for colleagues, students, and friends. On top of being an esteemed and tireless researcher, he was very interested in the world and culture, a polyglot, and was a great traveller. Out of science, his life was studded with intense sporting activity. He was a fencing and ski instructor, and he had an immense passion for the sea: he was vice president of the Naval League of Padua and one of the founders of the Diving Club. It is not only because of his tryptophan research contributions and scientific legacy that we would like to remember him by, but also because of his reassuring smile, sharpness, and passion for life.

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