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EDITOR PROFILE

Editor Profile: Nektarios Tavernarakis

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In this special interview series, we profile members of *The FEBS Journal* editorial board to highlight their research focus, perspectives on the journal and future directions in their field. Nektarios Tavernarakis is Chairman of the Board of Directors at the Foundation for Research and Technology-Hellas (FORTH), and Professor of Molecular Systems Biology at the University of Crete Medical School, Greece. In 2020, he was elected Vice President of the European Research Council (ERC). He has served as Editorial Board Member of *The FEBS Journal* since 2018.

Can you give an overview of your research group's major focus and goals?

Our research mainly focuses on the molecular mechanisms and cellular signalling pathways governing neurodegeneration, and ageing. Ageing is associated with a marked decrease in neuronal function and increased susceptibility to neurodegeneration. In human populations, this is manifested as an ever-increasing prevalence of devastating neurodegenerative conditions, such as Alzheimer's and Parkinson's disease, stroke, several ataxias and other types of dementia. The development of therapeutic interventions against these maladies, which are a major contributor to human disability in modern societies, has thus become a pressing priority. Although age-related deterioration of the nervous system is a universal phenomenon, its cellular and molecular underpinnings, nonetheless, remain obscure and progress in developing effective preventive or therapeutic interventions to combat neurodegenerative conditions has been markedly slow.

Our efforts concentrate on a fundamental question of modern ageing research: What mechanisms underlie age-related neuronal function decline? Through these studies, we aim to expand our understanding of age-related neurodegeneration, and provide critical insights with broad relevance to human health and quality of life.

What's been your favourite personal breakthrough, to date? How did you feel when you made this discovery and realized the wider implications?

Recently, we investigated the pathophysiology of heat stroke and uncovered a universal and potent protective mechanism against neuronal necrosis, triggered by extreme temperature and multiple other insults. During heat stroke, when the core body temperature can rise in excess of 40 °C, widespread cell death and consequent multi-organ failure can be triggered, and this is often fatal. The nervous system is particularly vulnerable, and heat stroke survivors commonly suffer permanent neurological damage. In recent years, the intensification of heat waves because of climate change has caused a surge of heat stroke fatalities throughout the globe. Although heat-related pathologies such as heat stroke are estimated to soon become one of the most serious causes of mortality, the cellular and molecular mechanisms responsible for the direct cytotoxicity of heat are not well-understood. This is partly due to the lack of appropriate models, where the direct effects of heat on cell function and survival can be studied at the organismal level, independently from secondary physiological and inflammatory responses.

To overcome these obstacles, and to tackle the molecular basis of heat cytotoxicity, we have established a model of heat stroke in the simple nematode

worm *Caenorhabditis elegans*. This model faithfully recapitulates cellular pathology following heat stroke in mammals, indicating its potential clinical relevance. Exposure of nematodes to extreme temperature causes extensive necrotic cell death, simulating cases of heat stroke in humans. While searching for protective mechanisms against this type of death, we discovered that pre-emptive activation of the highly conserved heat shock response pathway had a strong protective effect against necrosis. This pathway converges on a specific subcellular organelle, the Golgi apparatus, to preserve its function as a calcium storage and homeostasis compartment, under conditions of extreme stress. It is the first time that this organelle is directly implicated in necrosis. Importantly, this strong protective mechanism is both ubiquitous and universal. In addition to nematode, mammalian neurons are also shielded against necrotic death triggered by hyperthermia. Moreover, activation of the heat shock response generally and potently suppresses necrosis inflicted by diverse insults, unrelated to heat, such as hypoxia and excitotoxicity prevalent in stroke, and protein aggregation, implicated in neurodegenerative disorders. These findings reveal new players in the process of necrotic cell death and highlight the protective effect of an endogenous stress response pathway, with the capacity to defend against heat cytotoxicity and multiple other necrotic insults.

Another recent line of research in our laboratory culminated in the identification and characterization of an intricate molecular mechanism that coordinates the biogenesis and selective elimination of mitochondria, to regulate cellular energy homeostasis during ageing. Alterations in mitochondrial number, morphology and function heavily impact cellular metabolism and critically influence organismal physiology, health and lifespan. Mitochondrial dysfunction is a major hallmark of ageing and age-related neurodegenerative diseases. Therefore, the maintenance of cellular and organismal homeostasis necessitates the tight regulation of mitochondrial biogenesis, balanced with the removal of damaged mitochondria. Mitophagy is a selective type of autophagy that mediates the elimination of dysfunctional or aged mitochondria, and is the major mechanism by which cells regulate their mitochondrial content in response to stress or metabolic state. How cells coordinate the two critical and opposing processes of mitochondrial biogenesis and mitophagy to maintain cellular and organismal energy homeostasis was a mystery. We discovered a sophisticated molecular pathway that tightly links mitochondrial biogenesis with mitophagy, to preserve energy homeostasis and promote longevity. The accumulation of damaged or

superfluous mitochondria causes oxidative stress, initiating a dual retrograde response that orchestrates the induction of both mitochondrial biogenesis and mitophagy. This closed feedback loop preserves mitochondrial quality by neutralizing damaged, and generating fresh and healthy mitochondria, thus promoting longevity. Importantly, coordination of biogenesis and turnover of mitochondria enables cells to adjust their mitochondrial content, in response to physiological demands. Age-related decline of mitophagy both hinders removal of damaged mitochondria, and impairs mitochondrial biogenesis, instigating aberrant accumulation of mitochondria. The tight evolutionary conservation and ubiquitous expression of the regulatory factors involved in this highly coordinated response suggest that similar pathways uphold mitochondrial homeostasis to modulate lifespan, across diverse organisms including humans.

What research thread in your laboratory are you currently most excited about?

Currently, we are investigating the molecular mechanisms of necrotic neurodegeneration. Ageing increases susceptibility to neurodegeneration. Necrosis plays a role in devastating human pathologies such as stroke, ischaemia and age-associated neurodegenerative disorders. The mechanisms that govern necrotic neurodegeneration and its modulation by ageing are poorly understood. Autophagy has been implicated in necrosis and neurodegeneration, with both pro-survival and pro-

death roles. Autophagic flux declines with age, while induction of autophagy enhances longevity under conditions such as low insulin/IGF1 signalling and dietary restriction, which extend lifespan across diverse taxa.

Our recent findings indicate that organelle-specific autophagy, including mitophagy, pexophagy and nucleophagy, is an important, evolutionarily conserved, determinant of longevity. We are now dissecting the molecular underpinnings of neuron vulnerability to necrosis during ageing, focusing on cargo-specific macroautophagy. To this end, we are implementing a multifaceted approach that combines the power and versatility of *C. elegans* genetics with advanced, *in vivo* neuronal imaging and microfluidic technologies. We monitor autophagic flux of organellar cargo during neurodegeneration and under conditions that alter lifespan, with the aim of identifying mediators of organelle-specific autophagy in neurons. In addition, we conduct genome-wide screens for modifiers of age-inflicted neurodegeneration, and interrogate nematode models of human neurodegenerative disorders for organelle-specific autophagy and susceptibility to necrosis, upon manipulations that alter lifespan. We are also assessing the functional conservation of key mechanisms in mammalian models of neuronal necrosis. We anticipate that, together, these studies will deepen our understanding of age-associated neurodegeneration and pathology.

What are the key ongoing challenges in your field and can you discuss ways that these might be addressed?

The explosive progress in the life sciences that we are witnessing in recent years is fuelled by technological and engineering advances, in diverse fields of study. For example, nowadays biomedical research extensively benefits from developments in physics, chemistry, mathematics, computer science and informatics, as well as social sciences. In some cases, boundaries between domains and fields are fading. I have a strong appreciation of this interdisciplinary nature of modern research, which is needed to make real progress towards addressing important challenges in biomedical research.

One such challenge in the broad field of neurodegeneration and ageing pertains to the mechanisms maintaining long-term homeostasis in neurons. Neuronal cells are among the most long-lived, post-mitotic cells that survive and function efficiently for several decades. As such, they are critically dependent, perhaps more than any other cell type, on proper mitochondrial function. Thus, maintenance of neuronal energy homeostasis necessitates a tight regulation of mitochondrial quality control. How these cells preserve their pristine function and their overall homeostasis for so long is a challenging question. A more general related question pertains to the mechanisms that dynamically regulate neuronal metabolism in the adult mammalian brain.

Another focal issue is that of the deterioration of cellular organelle structure and function during ageing, which has been linked to human pathologies. For example, progressive and pronounced deterioration of nuclear architecture, coupled with marked expansion of the nucleolus, are common and conserved features of ageing, progeria and numerous other age-associated disorders. However, the molecular and cellular mechanisms that bring about these changes remain obscure. In addition, it is unclear whether such alterations are simply a corollary of the ageing process and age-related pathology, or have a causative role in senescent decline. Moreover, the contribution of major pathways that modulate lifespan, including insulin/IGF1 signalling and dietary restriction, towards shaping the nucleus during ageing is not understood.

I would also note the fundamental dichotomy between somatic ageing and germline immortality, in metazoans. Unlike somatic cells, the germline is a virtually immortal lineage and fulfils the pivotal task of protecting and faithfully transferring genetic material across generations. The molecular basis for bridging these two diametrically opposed phenomena, in biology, remains largely elusive. In addition to germ cells, this question also bears relevance to the mechanisms that sustain stemness and stem cell niche homeostasis.

Have you always been interested in science and was it inevitable that you would end up in this career? Were there any particular events, influences or mentors that shaped your research direction?

As far back as I can remember, I was always driven by an insatiable curiosity to understand the inner workings of the world. Admittedly, sometimes maybe a bit too much for my own well-being! I recall vividly my childhood attempts to build a Tesla coil and the painful experience of coming in contact with lethal high voltages. I also remember the joy I felt, when it finally worked and generated spectacular arcs!

To a great extent, I owe what I have accomplished so far to the brilliant teachers and mentors I was fortunate to have throughout my career, as well as to my parents who, appreciating the value of education and knowledge, encouraged me to pursue this path. One of

my early mentors was Fotis Kafatos, the founding President of the European Research Council (ERC). I consider proper mentoring as the most important factor for a successful career in academia and research. After completing my graduate studies at the Aristotle University of Thessaloniki, where I had the good fortune to be taught by highly motivated professors, I pursued my doctoral studies at the University of Crete. I was again fortunate to perform my PhD research at the neighbouring Institute of Molecular Biology and Biotechnology (IMBB), of the Foundation for Research and Technology – Hellas (FORTH), where Fotis was Director, at the time, before he left to become Director General at the EMBL. I was extremely lucky to work with scientists of such calibre, and become embedded in a vibrant research ecosystem, located in my home city, Heraklion. Following a few years of postdoctoral research in the United States, I came back as an independent researcher at IMBB and a professor at the Medical School of the University of Crete. Starting my independent career in Greece's premier research institution has been a milestone that afforded me the opportunity to pursue my ideas and build a productive research group in a multidisciplinary environment.

How do you balance management of your research group with your other academic and professional commitments?

I have been fortunate to collaborate with highly motivated and talented colleagues, students and postdocs since I started my career as an independent researcher. This has made it, not only easier, but also more enjoyable to run the laboratory. My teaching commitments at the University of Crete provide me with the opportunity to interact with students who are just embarking on a journey in science, which is truly rewarding.

In recent years, I have also been involved in administration; first, as Director of IMBB and, currently, as Chairman of FORTH. FORTH is the premier multidisciplinary research institution of Greece, with eight diverse institutes, including IMBB, and presence throughout the country. Running a large research organization is a demanding endeavour that requires persistence and personal commitment. Combining research, teaching and administration is challenging, and maintaining an overall balance can be quite difficult at times. Nevertheless, I believe that these activities, which may ostensibly appear competing, can actually be complementary. In my view, effective leadership of a research organization benefits from hands-on involvement in research and teaching. You have a much better understanding of the issues and the problems that need to be addressed at the administrative level if you are experiencing them first hand in your own laboratory.

What advice can you offer an early-career researcher who is hoping to forge a successful career in academia?

The trivial point to make would be that for a successful carrier in science, you need to follow the research direction, topic or field you really love the most. But, I don't think that it is even close to being the most important factor, or prerequisite. It is difficult to know, early on, what will get you excited down the road, especially if you don't yet know what is out there. Instead, in my view, it is very important to be receptive to new developments, new knowledge, and to cast a wide net. Dare to delve outside your comfort zone, don't be dismissive. You never know what might be just around the corner that will become your favourite line of research for the years to come.

I believe that another overarching determinant for success in science is curiosity. Ask, yourself, do you have an innate desire of finding things out, do you find pleasure in understanding, in discovering how nature works? Is pure, childlike curiosity still a strong driving force? If the answer to these questions is yes, then science and research are among the potential paths of life for you. Of course, persistence and patience are important qualities that will help you persevere through the disappointment of inevitable failures. But, if the motive is solving the puzzle, if curiosity is unquenched, in the end, you will likely figure out a solution to the problem. Where there is a will, there is a way.

You are a long-standing member of the Editorial Board of the FEBS Journal. In what ways do you think that the journal stands out from other journals in the Biochemistry & Molecular Biology sector?

The *FEBS Journal* is the premier journal of the Federation of European Biochemical Societies. FEBS is a grass roots, molecular life sciences organization, the largest in Europe, representing and supporting the biochemistry and molecular biology community. As such, *FEBSJ* is a journal run by scientists, for scientists, and this is something I appreciate very much. Moreover, the journal has become established as a high-quality publication venue that reaches a wide, international

readership, beyond Europe. I should also note that, in addition to offering an effective route for dissemination of research findings, the *FEBS Journal* contributes substantially by providing financial support to important communal programmes and services of FEBS, such as the annual FEBS Congress, the FEBS advanced courses and the FEBS fellowships. These programmes have become solid European traditions, and investing income generated by the *FEBS Journal* back to the community is having considerable and broad impact on biosciences in Europe and beyond.

Do you have a favourite FEBS Journal paper?

If I had to single out one paper, it would be an early review article written by Helmut Sies. The article was published in 1993 – back when the *FEBS Journal* was the *European Journal of Biochemistry* – with the title 'Strategies of antioxidant defence' (Sies H., *Eur. J. Biochem*., 1993, 215: 213–219). I was a graduate student at the time, working on gene expression regulation in *Saccharomyces cerevisiae*. The article reviewed molecular mechanisms of countering or adapting to oxidative stress. It prompted me to start looking into the biology of stress, and the cellular strategies that have evolved to defend against both intrinsic and extrinsic stressors. Living systems are always under stress, and stress response mechanisms are integral to life itself. At the time, this realization influenced me decisively to follow a research direction relevant to organismal stress physiology, for my postdoctoral studies. To a large extent, these studies led to one of the paths we are currently pursuing in the laboratory, which links cellular stress response mechanisms and homeostasis to ageing and neurodegeneration.

What long-lasting impact will the COVID-19 pandemic have on science and the public's perception of it, in your view?

The COVID-19 pandemic has made it abundantly clear that global policy-making strategies should prioritize investment in frontier blue skies research. Today, more than ever, the need for the support of bottom-up, basic and applied research is even more relevant. It is this strategy that stands any chance of protecting us in the face of unpredictable threats, such as SARS-CoV-2, and is best poised to address the diverse and complex challenges our world is confronted with. Take, for example, the RNA vaccines that were recently developed and found to be more than 90% effective against the coronavirus. The technology on which they are based is the result of more than 20 years of basic research into RNA biology. There would have been no way a vaccine could have been developed in just a few months, without such prior effort. We owe this unprecedented vaccine development success to the long-term investment in the basic research that preceded it.

Likewise, the CRISPR-Cas technology, which was recently awarded Nobel Prize in Chemistry, is based on fundamental observations in humble bacteria, dating back to the late 1980s. No one suspected at that time the immense progress that would follow the initial discovery, more than 20 years later. This goes to show how invaluable curiosity-driven research is for human societies, to overcome unexpected challenges ahead. Neglecting, or putting frontier research in the back seat, is a short-sighted strategy that would certainly spell disaster for humanity in the long run. A balanced investment in both fundamental and applied research is a sure-fire strategy towards generating impactful outcomes for society. Frontier research is the bedrock of innovative and transformative technological progress.

Moreover, substantial and long-term investment in frontier research is a prerequisite for achieving sustainable development goals. Approaching these objectives and battling unpredictable existential threats, akin to the current pandemic, are in my view among the major global and European challenges for the future. Rising up to these challenges will require the concerted efforts of scientific communities across the globe. We are already witnessing such spontaneous, bottom-up global coordination of research activities in response to the COVID-19 crisis. In a very short period of time, the virus and its *modus operandi* have been characterized in great detail, and we even now have highly efficient vaccines and therapeutics. This is a truly amazing feat and speaks volumes about the power and value of scientific research. Moreover, the technological advancements that are ushering in the new era of the 4th Industrial Revolution are the product of frontier research conducted decades ago.

To support basic and applied research, it is critical to intensify investment in science education, and to consider thoroughly and wisely the ethical implications of innovative, cutting-edge technologies that are being developed at an unprecedented pace.

Finally, can you tell us something about yourself that we might be surprised to hear?

I am an active radio amateur; I enjoy communicating over the radio waves with other radio amateurs from

all over the world. My callsign is SV9IOR. Electronics has been my hobby since my preschool years. In the era of ultra-wideband Internet and advanced cell phones, operating a short wave transceiver, using Morse code, to reach people in other continents provides an unmatched sense of nostalgia. I also enjoy very much building and repairing electronic equipment, such as radio transmitters and receivers, audio amplifiers or anything else I can get my hands on. In fact, biology was not my first career choice. When I was a high school student, I wanted to pursue studies in physics, or electrical and computer engineering. My initial plans notwithstanding, I came to appreciate biology, guided by the inspiring tutelage of my university professors. What also helped was that, to my eyes, biochemical pathways bore an uncanny resemblance to electronic circuits.

Ultimately, the intricacies of living matter won me over, and my excitement about the mystery of life has been growing ever since. Looking back now, I can safely say that following this path was probably one of the best choices I have made. It has been a very rewarding journey. We are currently witnessing colossal progress in all fields of biomedical research, and I am eager to see what is next in store.