LABORATORY OF AGEING AND NEURODEGENERATION
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BACKGROUND

We use the soil-dwelling, nematode worm Caenorhabditis elegans to investigate the molecular mechanisms of ageing and neuronal function. With its extremely well described nervous system of just 302 neurons, the worm offers a unique platform for such studies. One particular advantage of C. elegans that often goes unappreciated is the ability to obtain viable mutants with severely impaired neuronal function, or with extensive neuronal loss. Furthermore, these mutants can be studied genetically, thus increasing - sometimes decisively - the suitability of this organism towards dissecting neuronal development and function. Despite its minimalistic nervous system, C. elegans exhibits a rich repertoire of sensory capacities and behaviors. Such wide spectrum of easily discernible phenotypes can be exploited using the sophisticated genetics and molecular biology tools developed for the worm, to elucidate the molecular mechanisms underlying the wonderful faculties of the nervous system. We build on these exceptional features, focusing on three major research topics:

1. **Ageing and energy metabolism**
2. **Neurodegeneration/Necrotic cell death**
3. **Sensory transduction and integration**

Our group at the Institute of Molecular Biology and Biotechnology was the first to commence C. elegans research in Greece, about three years ago. Introduction of a new model organism, coupled with the relative geographic isolation of Crete, somewhat hinders much-needed interaction with other colleagues in the field. To bridge this gap and to also establish our presence within the European community of Neuroscience and C. elegans researchers, we have set up and maintain two powerful server clusters that host the two main nematode online resources, WormBase (ACeDB) and the C. elegans WWW Server, locally at IMBB (http://wormbase.imbb.forth.gr/ and http://elegans.imbb.forth.gr/). This facility is the European web mirror, the only one outside the US, and provides effortless and fast services to the whole European area and regions of Asia. In addition, we have organized and are coordinating an EU 6th Framework Programme Consortium of C. elegans researchers (named NemaGENETAG), aiming to generate a genome-wide collection of transposon-tagged mutants. This valuable resource will also be useful to non-C. elegans researchers and will become available worldwide (for more information on this ambitious initiative see http://elegans.imbb.forth.gr/nemagenetag/). In addition, we are participating in the EU 6th Framework Programme Consortium named TransDEATH, with the central strategy of following a trans kingdom approach to matters of cell death (see https://www.transdeath.org/index.php/Main_Page). Furthermore, we have constructed and continuously update an extensive web site for our laboratory, detailing our activities and providing information about the lab and worldwide C. elegans research (http://www.imbb.forth.gr/worms/).

RESEARCH ACTIVITIES

Our research focuses around the topics of necrotic cell death/neurodegeneration, ageing, and sensory transduction/integration. We are approaching these seemingly unrelated but intimately linked themes using the nematode Caenorhabditis elegans as a model organism. Our broad objectives are the following:

1. Elucidation of the molecular mechanisms of necrotic cell death.
2. Elucidation of the role of protein synthesis in ageing and senescent decline.
3. Elucidation of the molecular mechanisms of sensory transduction and integration by the nervous system.
4. Development of novel genetic tools for C. elegans research.

1. Molecular mechanisms of necrotic cell death. Two commonly occurring patterns of cell death have been described: apoptosis and necrosis. Apoptotic death generally occurs as part of normal development and in cell depletion due to a broad range of stimuli, usually mild in nature. The second pattern of cell death, necrosis, occurs in response to extreme changes of physiological conditions or is a result of genetic abnormalities. Various cellular insults, including hyperactivation of ion channels such as the degenerin channels mentioned in the previous paragraph, expression of human beta-amyloid protein implicated in Alzheimer's disease, constitutive activation of certain G proteins and possibly the ageing process, can trigger a degenerative, necrotic-like cell death in Caenorhabditis elegans. This suggests that diverse initiating stimuli can induce a common death mechanism in injured cells. We are genetically and molecularly deciphering the Caenorhabditis elegans necrotic death program. Towards this end we have identified several novel genes that are required for necrotic-like cell death. Since most Caenorhabditis elegans genes have counterparts in higher organisms and since the apoptotic cell death program has been conserved from nematodes to humans, it is highly likely that mechanisms of degenerative cell death are similarly conserved. Thus, our efforts boast the important corollary of potentially providing new insights into brain injury and disease.

2. Ageing, senescent decline and the role of protein turnover. Protein synthesis and degradation are the two essential interlinked cellular processes responsible for maintaining a functional protein content in every cell. A decrease in protein turnover is associated with senescent decline and ageing. In addition, caloric restriction, a feeding regimen that confers longevity, in which calorie intake is reduced without limiting vitamins, minerals and other essential nutrients, increases protein turnover. However, a direct molecular link between ageing and regulation of protein turnover has not been established. We exploit the experimental strengths of the Caenorhabditis elegans model system in an effort to identify the specific biochemical steps underlying alterations of protein turnover during ageing and under caloric restriction. Our testable working hypothesis is that the delicate balance between detrimental protein modification and protein turnover that exists early in life is tipped in favor of deleterious protein modification during late stages of life. The rate at which a protein pool is refreshed at any given point in time is determined by the rate of protein synthesis and protein degradation at that particular point. Protein turnover cannot keep up with ever-increasing accumulation of damaged proteins during ageing. Increased protein turnover might consequently be one of the major causes of lifespan extension under caloric restriction or in long-lived mutants, by facilitating the maintenance of a fresher pool of proteins with less accumulated damage. Work with powerful genetic models that can be easily engineered such as Caenorhabditis elegans, should enable direct testing of the hypothesis that modulation of protein turnover rates is critical in lifespan and is a required component of caloric restriction. Our investigation focuses on the determination of those mutable steps of protein synthesis and degradation that can be altered to affect longevity and is certain to provide novel insight into the molecular mechanisms of ageing and cell survival. The molecules enacting these steps could constitute attractive pharmacological targets for therapeutic reversal of senescent decline.

3. Molecular mechanisms of sensory transduction and integration. In all organisms, the nervous system receives information about the environment via specialized sensory organs. This information is then processed and integrated to produce relatively permanent changes in future behavior. These changes of future behavior that reflect past experience are the manifestation of memory. The molecular mechanisms that underlie these changes are poorly understood. The nematode C. elegans with its fully charted simple nervous system of 302 neurons offers a unique platform in which to study these mechanisms. We aim to identify genes required for the sensory transduction and integration that forms the basis of learning and memory in the nematode. Members of the DEG/ENaCs superfamily of ion channels have been identified in nematodes, snails, flies and vertebrates including humans, where they serve diverse functions such as ion homeostasis and sensory transduction. Mechanotransduction is the process by which mechanical energy is converted into cellular signals, and is essential for hearing, balance, touch, and for regulating muscle contraction and blood pressure. A long-standing problem in the mechanotransduction field has been that genes encoding mechanically-gated channels eluded cloning efforts, resulting in a large gap in our understanding of their function. We and others have identified specific DEG/ENaC proteins that are hypothesized to normally function as the central mediators of touch transduction and proprioception (how the body maintains coordinated movement) in Caenorhabditis elegans. These mechanically-gated channels are postulated to be tethered to both the extracellular matrix and to the cytoskeleton, linkages that serve to deliver gating tension to the channel. We are currently combining genetic, molecular and biochemical approaches to determine and compare the composition/regulation of mechanosensitive channel complexes in nematodes. Members of the acid-sensing subgroup of DEG/ENaC ion channels (termed ASICs) have been implicated in synaptic plasticity, learning and memory in mammals. We find that ASIC-1, a novel DEG/ENaC protein and a close homologue of mammalian ASIC, is highly expressed in head sensory neurons and interneurons. ASIC-1 is required for conditioning to several chemical attractants, while it is dispensable for chemotaxis. Consistently, this gene is also required for associating the presence of food with the rearing temperature. Such observations indicate that DEG/ENaCs contribute to the capacity of the animal for associative learning. Therefore, ASIC roles in associative learning and memory might be conserved from nematodes to mammals, thus, making C. elegans an attractive model in which to dissect the relevant mechanisms.

4. Development of novel genetic tools. The nematode Caenorhabditis elegans is a widely appreciated, powerful platform in which to study important biological mechanisms related to human health. More than 65% of human disease genes have homologues in the C. elegans genome, and essential aspects of mammalian cell biology, neurobiology and development are faithfully recapitulated in this organism. We aim to develop cutting-edge tools and resources that will facilitate modeling of human pathologies in C. elegans, and advance our understanding of animal development and physiology. Specifically, we are optimizing and automating existing transposon-mediated mutagenesis methodologies based on the Mos1 transposable element, in addition to developing alternatives using the PiggyBac and Minos transposon systems. Together with 5 collaborating European laboratories, we will exploit these tools to generate and evaluate a collection of transposon-tagged mutants, aiming to cover the complete genome of approximately 20,000 genes.

Representative Publications

1. Syntichaki P. Troulinaki K. and Tavernarakis N. (2007). eIF4E function in somatic cells modulates ageing in Caenorhabditis elegans. Nature, 445: 922-926.

2. Voglis G. and Tavernarakis N. (2006) The role of synaptic ion channels in synaptic plasticity. EMBO Reports, 7: 1104-1110.

3. Syntichaki P., Samara C. and Tavernarakis N. (2005) The Vacuolar H+-ATPase mediates intracellular acidification required for neurodegeneration in C. elegans. Current Biology, 15: 1249-1254.

4. Syntichaki P. and Tavernarakis N. (2003) The biochemistry of neuronal necrosis: Rogue biology? Nature Reviews Neuroscience, 4: 672-684.

5. Syntichaki P., Xu K., Driscoll M. and Tavernarakis N. (2002) Specific aspartyl and calpain proteases are required for neurodegeneration in C. elegans. Nature, 419: 939-944.

6. Syntichaki P. and Tavernarakis N. (2002) Death by necrosis: Uncontrollable catastrophe or is there order behind the chaos? EMBO Reports, 3: 604-609.

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