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Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project:
DNA Damage & the Innate Immune Response in Health and Disease

Principal Investigator:
George A. Garinis

Reader-friendly title:
DNA damage and inflammation

Scientific Area: Genetics

Institution and Country:
Institute of Molecular Biology & Biotechnology

Host Institution:
FORTH

Collaborating Institution(s):

Project webpage:
www.garinislab.gr


Inspire


The Garinis lab

Budget: 180.000 euros

Duration: 36 months

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Research Project Synopsis

Genome maintenance and immune defense strategies are closely coordinated and appropriately mobilized in a circumstantial and contextual manner. The slow but steady buildup of damaged cells within tissues is expected to intensify DNA damage response (DDR) signaling and DDR-mediated pro-inflammatory signals over time perpetuating a vicious cycle events leading to chronic inflammation, tissue malfunction and degeneration during old age. However, it has been challenging to delineate how DNA repair and the DDR are functionally linked to innate immune signaling. More work is also necessary to define the immune mediators linking nuclear DNA damage sensors with innate responses in the cytosol, whether DDR-driven immune responses affect organismal survival over time or to what extent such mechanisms can be used to target cells with aberrant genomes during senescence or in cancer. Here, we propose a multidisciplinary research strategy combining our expertise in mouse genetics with advanced high-throughput approaches to assess the causal contribution of persistent DNA damage in innate immune responses, to delineate the functional links between DNA damage sensing and innate immune signaling, to dissect the functional role of DNA damage-driven inflammation in health and disease.

Project originality

INSPIRE builds upon novel scientific paths and the conceptual advance that health span can substantially be extended if we gain significant insights into the mechanisms that drive age-related pathology. INSPIRE brings in a research group with proven excellence in the proposed research topic, state-of-the art tools and a unique series of mammalian models to address fundamental concepts and therapeutic approaches aiming at combating age-related organismal decline. The program has its core intellectual focus on the causal contribution of DNA damage on chronic inflammation and its functional links to age-related metabolic reprogramming, cellular malfunction and organismal decline over time. Specifically, the proposed research strategy is designed as a multilayered approach to develop knowledge on the impact of irreparable DNA lesions on the activation of innate immune signaling and their therapeutic use for a wide range of debilitating diseases associated with old age. In this context, INPIRE is thought-provoking, challenging and entirely novel.

Expected results & Research Project Impact

Ageing is an inexorable homeostatic failure of complex but largely unknown etiology that leads to increased vulnerability to disease (e.g. cancer, diabetes, musculoskeletal and cardiovascular diseases, immune-senescence neurodegeneration) with enormous consequences on the quality of individual lives and the overall cost to society. Human efforts over the last centuries have succeeded in substantially lengthening lifespan, allowing ageing to become a common feature of western societies. It has been, however, significantly challenging to unravel the molecular basis of the processes that cause loss of bodily functions and degeneration of cells and tissues with advancing age. The discouraging complexity of the ageing process, the noticeable lack of tools to study it, and a shortage of experimentally tractable model systems have greatly hindered any testable hypothesis-driven approaches to understand the molecular basis of ageing, particularly in mammals. It is now widely accepted that ageing is evolved by limitations in somatic maintenance, resulting in the gradual build-up of indiscriminate macromolecular damage accumulation, stem cell exhaustion, deregulated nutrient sensing, metabolic, epigenetic and structural changes as well as loss of proteostasis and altered intercellular communication. However, an accumulating body of evidence also suggests that ageing is subject to regulation by evolutionarily highly conserved molecular pathways. Thus, macromolecular damage may drive the functional decline with ageing; however, a battery of longevity assurance mechanisms may set the pace on how rapidly damage builds up and function is lost over time. The impetus for the proposed line of research is based on the magnitude of the DNA damage-driven pathologies in Western societies: cancer and aging. This is clearly justified by the increasing cancer incidence problem of the elderly and the continuously expanding European aging population (Figure 19). Intensive research is, therefore, greatly needed across the scientific spectrum of genome maintenance and DDR mechanisms.

The importance of this funding

At present, H.F.R.I. funding is one of the few funding schemes available to the Greek academic community and perhaps the only one that has regular yearly calls. So far, H.F.R.I. has been a tremendous support for our lab, our work and the people involved while it has lay down the basis to provide with preliminary data and attract further funding.

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