complemented with additional datasets produced in-house and integrated with proteomics and translatomics data to comprehensively provide insight into the aging phenotype and underlying biological mechanisms. This work was supported by the Portuguese Foundation for Science and Technology (FCT) (iBiMED: UID/BIM/04501/2020; MF: SFRH/BD/131736/2017; SF: SFRH/BD/148323/2019) and by European investment funds (FEDER) through COMPETE 2020 (GenomePT: POCI-01-0145-FEDER-022184; MEDPERSYST: POCI-01-0145-FEDER-016428-PAC; WISDOM: POCI-01-0145-FEDER-029843), and through CENTRO 2020 (pAGE Integrated project: Centro-01-0145-FEDER-000003; MEDISIS: CENTRO-01-0246-FEDER-000018).

Biomedicine

Unraveling the molecular mechanisms deregulated in response to LAP1 dysfunction

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Lamina-associated polypeptide 1 (LAP1) is a ubiquitous transmembrane protein that resides in the nuclear envelope (NE), a highly organized double membrane that encloses the eukaryotic genome. In the last decade, several mutations in the human LAP1-encoding TOR1AIP1 gene were associated with clinical phenotypes that range from tissue-specific disorders (muscular dystrophy, cardiomyopathy and/or dystonia) to a multisystemic syndrome. Despite increasing evidence for the pathogenicity of LAP1 deficiency, the physiological functions of this protein remain poorly characterized. With the aim of getting new insights into LAP1's biological significance, patient-derived skin fibroblasts bearing the pathological LAP1 E482A missense mutation (reported in a case of severe dystonia, cerebellar atrophy and cardiomyopathy) and age-matched control skin fibroblasts were used to investigate the molecular consequences of human LAP1 depletion. Significant alterations in the protein levels and/or subcellular localization of LAP1, its known binding partners and other relevant NE/endoplasmic reticulum proteins were detected in patient-derived cells as compared to control ones. This work will permit to expand current knowledge on how LAP1 functionally operates, as well as to uncover which signaling pathways are deregulated in response to LAP1 dysfunction and, hence, could be targeted for the development of disease modifying therapies for LAP1-associated pathologies.

Biomedicine

Modulation of inflammation and the gut microbiota to improve ageing outcomes

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Ageing, one of the current main health challenges, is accompanied by numerous changes, including the development of a low level of chronic inflammation ("inflammageing") and dysbiosis of the gut microbiota. Yet, the contribution of these factors to the observed differences in frailty of the ageing population is unknown. Throughout ageing, microbiota dysbiosis and inflammageing influence each other in a positive feedback loop, whose onset remains unidentified.

This project proposes to investigate whether this feedback loop can be interrupted, and how this interruption can impact age-related signs.

To achieve this aim, we will use an animal model of ageing and reduce inflammation using compounds with anti-inflammatory properties. These animals will be further colonized with a labelled commensal strain of Escherichia coli. We will then explore the consequences of reducing inflammation by comparing the adaptive pattern of E. coli obtained in these conditions with the one obtained in the untreated control group. This will inform us on how reducing inflammation can impact microbiota dysbiosis and other age-related signs such as gut permeability, thus potentially improving the healthspan of the elderly population.

Biomedicine

Alzheimer's disease risk gene BIN1 specifically associates with common comorbidities

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With the world's population rapidly aging, the prevalence of Alzheimer's Disease (AD) is increasing, representing one of the leading causes of morbidity and mortality worldwide. Several genes have been identified as presenting risk for distinct pathological conditions among them AD. Genome-wide association studies identified the Apolipoprotein E (APOE) as the highest risk factor for AD and the Bridging Integrator 1 (BIN1) as the second highest. For the latter, the single nucleotide polymorphism (SNP) rs744373 is the one most frequently associated with AD risk. Given that other pathologies are increasingly described as important AD risk factors, the associations to comorbidities that these two genes (APOE and BIN1 rs744373 variant) confer, were addressed in a primary care-based study group, denoted pcb-Cohort. Regarding BIN1, data from the pcb-Cohort shows that with respect to dyslipidemia (DYS) cases, carriers of BIN1 risk allele G positive (rs744373 variant) were at a significantly lower