and function, neuronal cells were transfected with SIRT1 isoforms v1, v2 or v3 plasmids, respectively. Gene expression was measured by quantitative reverse transcription PCR (RT-qPCR). Our data showed SIRT1 isoforms v1, v2 and v3 differentially regulated PCG-1alpha and PCG-1beta, which are the upstream regulators of mitochondrial structure and function. SIRT1v1 upregulated mitofusin-1 (MFN1), the mitochondrial dynamin-like GTPase (OPA1) gene, and the transcription factor A mitochondrial (TFAM) gene. In contrast, the SIRT1-v2 isoform repressed the MFN1, MFN2, and TFAM genes, while the SIRT1-v3 isoform repressed the MFN1 gene. In addition, the three SIRT1 isoforms differentially affected the mitochondrial respiratory complex I genes, including NDUFAB1, NDUFS1, NDUFV1, NDUFV2. The data indicates that SIRT1 regulates mitochondrial biogenesis and function through a signaling pathway involving PGC-1alpha, PCG-1beta, mitofusin 1 and 2, OPA1, and TFAM genes. Taken together, alternative splicing generated three SIRT1 isoform proteins with diverse functions. Age-related changes in the alternative splicing events are likely to impact sirtuin-regulated cellular functions and signaling pathways in aging and senescence.

THE INTERPLAY BETWEEN STRESS RELATED GENES AND ITS ROLE IN HUMAN LONGEVITY: INSIGHTS FOR TRANSLATIONAL STUDIES

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Human lifespan is a multifactorial trait resulted from complicated interplay among many genetic and environmental factors. Despite substantial progress in clarifying many aspects of lifespan' variability the mechanism of its multifactorial regulation remains unclear. In this paper we investigate the role of genes from integrated stress response (ISR) pathway in such regulation. Experimental studies showed that persistent cellular stress may result in cellular senescence (for proliferating cells), or in apoptosis (for post-mitotic cells) which may affect health and lifespan in laboratory animals. These studies also showed which ISR genes are likely to interplay to produce joint effects on these traits. Note that in humans, the interplay between these genes does not necessarily influence these traits. This is because biological mechanisms regulating these traits in laboratory animals and humans may differ. This means that, when possible, the experimentally detected connections promising for human applications, should be verified using available human data before their testing in expensive clinical trials. In this paper we used HRS data to test connection between SNPs from the EIF2AK4 gene that senses cellular stress signals and the DDIT3 gene from the apoptosis regulation part of the ISR. We found genome wide significant associations between interacting SNPs from these genes and longevity. This result shows that available human data may be successfully used for making important steps in translation of experimental research findings towards their application in humans. Following this strategy may increase efficiency of clinical trials aiming to find appropriate medications to promote human health and longevity.

USING THRESHOLD REGRESSION AS AN APPROACH TO INCORPORATE INFORMATIVE MISSINGNESS IN LONG LIFE FAMILY STUDY DATA

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Genetics of aging is important since aging is a major risk factor in most diseases. Variables describing physiological state and cognitive functioning that influence morbidity and mortality risks can serve as biomarkers of aging. They change with increasing age and the ways in which these variables change can also influence these risks. Missing data due to dropout or death create problems in longitudinal studies producing biased results especially if the gap between exams is relatively long, as is the case in the Long Life Family Study (LLFS). We applied the threshold regression model to LLFS data to investigate the vitality and its rate, which are conceptualized as latent variables characterizing health and longevity, and to cope with such a problem. We performed genome-wide association study by sex and age groups to discover genetic signals on these phenotypes. We found 11 variants from the DACT2 gene, p-values < 1E-6 and variants rs12151399 (p-value = 8.43E-8, intron variant, gene AGAP1, in females), rs27958 (p-value = 8.39E-8, intron variant, gene ARHGAP26, in males) showing associations with the vitality. Olfactory receptors showed significant enrichment among the group of males over 80 years for the rate of aging phenotype. Results showed that vitality and its rate differ among sex and age groups. This work is an important step toward understanding the processes of aging linking the vitality with individual genetics using data from deceased and living individuals.

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A NOVEL PROBIOTICS THERAPY FOR AGING-RELATED LEAKY GUT AND INFLAMMATION

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Inflammaging characterized with increased low grade inflammation in older adults is common determinant of unhealthy aging; and is a major risk factor of morbidity and mortality in older adults. The precise origin of inflammation in older adults is not known, however, emerging evidence indicate that increased intestinal epithelial permeability (leaky gut) and abnormal (dysbiotic) gut microbiota could be one of the key source. However, no preventive and treatment therapies are available to reverse the leaky gut and microbiome dysbiosis in older adults. Here, we presented the evidence that a human-origin probiotics cocktail containing 5 Lactobacillus