Defective immune functions are key triggers of incidence and prevalence of age-related diseases, including infectious diseases and tumors. Previous works have reported that some food materials or constituents, for instance, prebiotics and probiotics, can improve immune defects; however, mechanistic linkages remain poorly understood. In this study, we demonstrate that our novel food constituent X may mitigate the age-related inflammatory phenotypes in various tissues, which is probably associated with the serum levels of pro-inflammatory cytokines. C57BL/6 mice at the ages of 16 (n = 45 mice) or 11 months (n = 20) were used as physiologically aged mice. The serum levels of pro-inflammatory cytokines, including interleukin-1β and interleukin-6, in aged mice were higher than those in 1-month-old young mice (n = 30). Correspondingly, inflammatory phenotypes were observed in various peripheral tissues of aged mice. Interestingly, serum levels of these cytokines were reduced by oral administration of X into aged mice for 6 months, which was seemingly responsible for suppression of the age-related inflammatory phenotypes in peripheral tissues. These results suggest that some food materials or constituents may potentially mitigate the age-related physiological defects through regulation of pro-inflammatory cytokines.

4-HNE-INDUCED INNATE IMMUNE RESPONSES INFLUENCE ANTI-CARCINOGENESIS IN ROS-OVERPRODUCED MODEL MICE

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Mitochondrial reactive oxygen species (ROS) which are mainly generated as an uncoupled consequence of electron transport cause the cellular and organismal oxidative stress. It has been previously demonstrated that the excessive mitochondrial ROS production caused by mitochondrial complex II SDHC mutation results in premature death in C. elegans mev-1 mutant (G71E) and D. melanogaster mev-1-mimic transgenic flies (171E), and excessive apoptosis and tumorigenesis in mouse embryonic fibroblast SDHC E69 cells (V69E) (M. Tsuda, et al. BBRC 2007, T. Ishii, et al. Cancer Res. 2005, N. Ishii, et al. Nature 1998).

In humans, it has been reported that some mutations in SDHB, SDHC or SDHD often result in hereditary and/or sporadic paragangliomas, gastrointestinal stromal tumors and pheochromocytomas (T. Ishii, et al. BBA 2013). Recently, Tet-mev-1 conditional transgenic mice have been established using our uniquely developed Tet-On/Off system, which can induce the mutated SDHC (V69E) coding gene to be equally and competitively expressed compared to the endogenous wild-type SDHC gene. The Tet-mev-1 mice experienced intracellular oxidative stress by mitochondrial respiratory chain dysfunction developed low birth weight, growth retardation, age-dependent corneal pathophysiological changes, low fertility, recurrent miscarriage and age-dependently disrupted memory consolidation with astrocyte defects (T. Ishii, et al. Mitochondrion 2011; H. Onouchi, et al. IOVS 2012; Y. Uchino, et al. PLoS ONE 2012; T. Ishii, et al. Redox Biology 2014; T. Ishii, et al. Aging Cell 2016).

Here, it has been demonstrated that lymphocyte accumulation which is chronically activated with age influences the anti-carcinogenesis of large-cell lung carcinoma with oxidative stress in Tet-mev-1 mice. In aged Tet-mev-1 mice, large-cell neoplastic cells were developed into the lymphocyte accumulation in lung. The lymphocytes which were associated with γδT cell activation leading to innate immune responses were initiated by o-6 fatty acid peroxidation-derived 4-hydroxy-2-nonenal (4-HNE). We propose that the 4-HNE-induced innate immune responses which associate with γδT cells involved in intraepithelial lymphocytes (IELs) may initially prohibit the oxidative stress-developed carcinoma.

PHYLOGENETIC GROUPS OF ESCHERICHIA COLI TO DIAGNOSE URINARY TRACT INFECTION IN GERIATRIC POPULATION

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Discrimination between urinary tract infection and urinary colonization is a frequent and difficult problem in geriatric population. E. coli is the most frequently isolated pathogen in urine in this population. Of the 8 known phylogenetic groups in the species, groups B2 and D are the most virulent and more frequently responsible for extra-intestinal infections, particularly urinary tract infections. However, there is no data on the distribution of these phylo-groups in the geriatric population. We conducted a study that included clinical data from the host and the phylogenetic group of E. coli to find criteria to differentiate infection and colonization. All E. coli-positive urine analysis from patients over 75 years of age and hospitalized at the Lariboisière hospital from 15 February to 15 May 2016 were included. The virulent phylogenetic groups (B2 and D) of E. coli are significantly more frequent in infection than in colonization in geriatric population (Odds Ratio: 3.05 (1.44–6.86), P = 0.005). However, to the bacterial virulence is added factors of fragility of the host allowing the development of an infection, such as the presence of altered autonomy (P <0.001), falls (p <0.001), dementia (p = 0.005), malnutrition (p = 0.001) and urinary pathology (p = 0.002).

TRANSCRIPTIONAL PROFILING OF HUMAN FEMORAL MESENCHYMEAL STEM CELLS IN OSTEOPOROSIS AND ADIPOGENESIS

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Genetic alterations are major contributing factors in the development of osteoporosis. Osteoblasts and adipocytes share a common origin, mesenchymal stem cells (MSCs), and their genetic determinants might be important in the relationship between osteoporosis and obesity. In the present study,
we aimed to isolate differentially expressed genes (DEGs) in osteoporosis and normal controls using human MSCs, and elucidate the common pathways and genes related to osteoporosis and adipogenesis. Human MSCs were obtained from the bone marrow of femurs from postmenopausal women during orthopedic surgeries. RNA sequencing (RNA-seq) was carried out using next-generation sequencing (NGS) technology. DEGs were identified using RNA-seq data. Ingenuity pathway analysis (IPA) was used to elucidate the common pathway related to osteoporosis and adipogenesis. Candidate genes for the common pathway were validated with other independent osteoporosis and obese subjects using RT-PCR (reverse transcription-polymerase chain reaction) analysis. Fifty-three DEGs were identified between postmenopausal osteoporosis patients and normal BMD controls. Most of the genetic changes were related to the differentiation of cells. The NR4A family was identified as possible common genes related to osteogenesis and adipogenesis. The expression level of the mRNA of NR4A1 was significantly higher in osteoporosis patients than in controls (p=0.018). The expression level of the mRNA of NR4A2 was significantly higher in obese patients than in controls (p=0.041). Some genetic changes in MSCs are involved in the pathophysiology of osteoporosis. The NR4A family might comprise common genes related to osteoporosis and obesity.

CHARACTERISTICS OF LATE-LIFE DEPRESSION RELATED WITH THE RISK OF INCIDENT DEMENTIA
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Objectives: The incidence rates and risk factors of dementia and Alzheimer's dementia were examined, with special focus on the relationship between baseline depression and incident dementia.

Methods: The present study assessed elderly individuals who resided in a rural community in Korea. After the baseline assessment (2008), there were two schedules for the follow-up (2009 and 2013). Sociodemographics, lifestyle characteristics, and clinical factors were examined; depression was evaluated using the Geriatric Depression Scale, Short form and cognitive diagnoses were determined by a psychiatrist using the DSM-IV criteria. A Cox proportional hazard model was used to determine the risk factors for dementia and factor analysis was conducted to classify depressive symptoms.

Results: Among 751 subjects at the baseline, those who were not diagnosed with dementia at baseline (N = 701) were followed up with for a mean period of 5.5 years. A total of 483 subjects were assessed during this follow-up period and 40 new cases of incident dementia (16.2 per 1000 PY) were identified. Baseline depression was not related with the risk of 5-year incident dementia. However, regarding the characteristics of depression, higher persistence and severity increased the incident dementia. Also, depression accompanied with dysexecutive function and the low energy component which may imply frontal lobe dysfunction increased the incidence of dementia.

Conclusion: Different relationship between depression and dementia according to different quantitative and qualitative characteristics of late-life depression suggest that the conversion process from depression to dementia may be the various ones, not the same one.

MODULATION OF HSF-1 LEVELS BY HIGH CHOLESTEROL AND ITS OXIDIZED PRODUCT 27-HYDROXYCHOLESTEROL
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Dietary intake may influence both aging and disease-related genes that increase Alzheimer’s Disease risk. Some diets may improve cognition and people highly adherent to the Mediterranean diet experience less hippocampal atrophy over time than those less adherent. Conversely, diets rich in saturated free fatty acids (sFFA) may increase AD risk. The mechanism of fat induced neurodegeneration includes neuroinflammation blood-brain barrier (BBB) disruption, phosphorylated Tau, and proteotoxicity. Thus, diets may either promote or delay aging and AD.

We examined the expression of the longevity and stress factor, Heat shock transcription factor 1 (HSF1), in a cholesterol – fed rabbit model of AD. In this model, we found that both the mRNA levels and the protein distribution of HSF1 are significantly decreased in rabbit hippocampi relative to age matched controls. Because 27-OHC levels are elevated by hypercholesterolemia, aging and oxidative stress, we examined in vitro effects of 27-OHC on astrocytes and found dramatic reductions in HSF1 protein levels in the absence of cell death.

Collectively, our results suggest that high cholesterol diets and its oxidized metabolites such as 27-OHC negatively impact a key longevity and cell protection factor, HSF1. Dysregulation of HSF1 by cholesterol and/or its oxidative by-products appears to be at the mRNA or transcriptional level, suggesting a heretofore unknown mechanism of HSF1 regulation. Because disturbances in cholesterol metabolism, oxidative stress, and aging are all risk factors for AD, our results provide new information that disruption of HSF1 may be a key link by which these factors lead to AD progression.

ABUNDANT NON-PLEIOTROPIC AND PLEIOTROPIC ASSOCIATIONS WITH AGE-RELATED TRAITS IN A MODEST SAMPLE
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Genome-wide association studies (GWAS) are traditionally based on principles of medical genetics. This strategy is well adapted for Mendelian disorders. Genetics of phenotypes that leave human organisms vulnerable to diseases in late life (called age-related phenotypes) is, however, more complex. The fundamental complicating factor is the elusive role of evolution in fixing molecular mechanism of these phenotypes. This complexity implies a special type of an inherent genetic heterogeneity reflecting sensitivity of genetic associations with age-related phenotypes to the life course of individuals in different environments. Here we follow a two-stage genome-wide approach that leverages this heterogeneity. This approach is demonstrated by examining non-pleiotropic and pleiotropic genetic predisposition to 24 age-related phenotypes (16 biomarkers, 7 diseases, and death) in a modest sample (N=26,371) from five studies (ARIC, FHS, MESA, CHS, and CARDIA) from the Candidate Gene Association