



The Aging Molecular Mechanism of Senescence-Accelerated Mouse and Anti-Senescence Molecular Mechanism of Traditional Chinese Medicine



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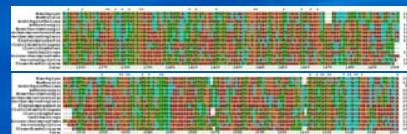
Aging is a progressive physiological changes in an organism that lead to senescence, or a decline of biological functions and of the organism's ability to adapt to metabolic stress. Senescence-Accelerated Mouse (SAM), a group of related inbred strains, has been established as a murine model for ageing study¹. The SAMP10/Ta strain mice have short life span and ageing-related deficits in learning and memory, emotional disorder and abnormal circadian rhythms. And SAMRITA strain mice have normal life span and no ageing-related disorders as control².

A better understanding of the molecular effects of ageing in the brain may help to reveal important aspects of organism ageing. As well as processes that lead to ageing-related brain dysfunction. We applied DDRT-PCR technology to investigate the ageing-specific expression genes of the murine cerebrum in three senescence-accelerated mouse (SAM) strains, SAMP8/Ta SAMP10/Ta and SAMRITA. From them, 14 age-specific expression gene fragments and 35 strain-specific expression gene fragments had been successfully cloned, most of which had been reported to be aging-related.

Among them, two aging-related gene cDNA full sequences, which we interested, had been cloned. Rab14, which is localized to both the biosynthetic (ER, Golgi, and TGN) as well as endosomal compartments, plays a role in biosynthetic as well as recycling pathways between the Golgi and endosomal compartments³. Unexpectedly, a new gene cDNA full sequence also had been cloned, which is highly homologous to rab14 cDNA sequence. We temporally named it rab14 variant, which deleted 54bp in its open reading frame that compared with the rab14 cDNA sequence of the same strain, and the deleted part sequence of the variant just located at the ATP/GTP binding site region of the rab14. This indicated that the function of the rab14 variant is different to the rab14, as the ATP/GTP binding site is essential for the rab14 function. The accurate function of this variant need to be further researched. The second cloned cDNA full sequence is of the SUV3L1, which is a helicase and exhibits multiple-substrate unwinding activity, and involving in RNA post-transcriptional processes, stability of transcripts, and damaged DNA repair. Further analyses found that there is a null mutation in its open reading frame, which may be the reason of the SAMP8 exhibiting senescence-accelerated pathophenotype.



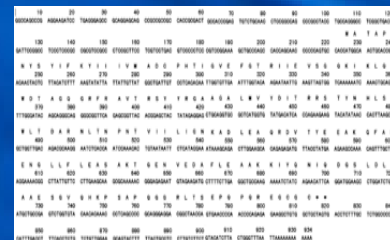
The figure shows the one year old SAM mice



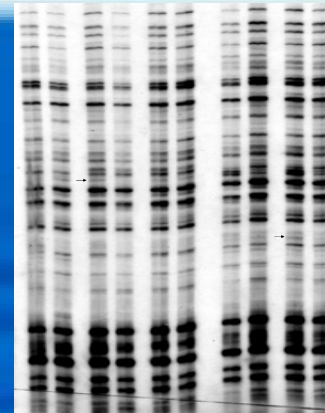
Part result of the suv311 cDNA sequence compared with other organisms



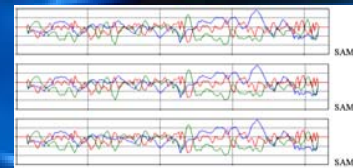
This is the evolution tree by comparing the suv311 cDNA



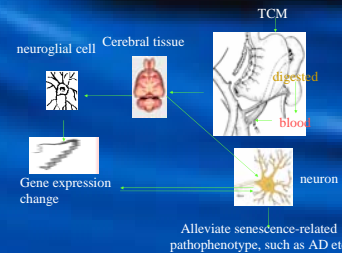
One of the rab14 variants cDNA sequence and it encode product sequence



This figure shows part of results of DDRT-PCR. The arrowheads show the DD bands



The 2nd Structure analysis of RAB14



Senescence is a common biological phenomenon in almost all organisms. In China, using the Chinese traditional medicine for anti-senescence has long history and had accumulated abundance of datum in clinic. In the 'herbal medicine of the agricultural god's scripture' (the first pharmacological book in China), 85 herbal medicines' function had been described to be anti-senescence. According to the Chinese traditional medicine theory, there are many Chinese traditional medicines have anti-senescence effects.

The Chinese traditional medicine 'Bushen Yinao Pian' (a complex prescription) has been used in clinic for anti-senescence, improving the learning and memory function over thirty years in China, and was known to be effective, but its mechanism is still elusive. By using DDRT-PCR to compare the gene expression changes of the SAM mouse cerebral tissues between the test group and control group, 43 differential expression gene fragments had been cloned. They are involving in energy metabolism, signaling transducer pathway, protein synthesis and degradation, RNA post-transcriptional process and stability of transcripts, and DNA replication and damaged DNA repair. Those indicated that the TCM exerts its integral effects with multi-gene, multi-target sites, and multi-effect mechanism in anti-senescence.

Up to date, two cDNA full sequences, the lrpap-1 and b-fabp, which we are interested, had been cloned. They express increased in the TCM given mice. The B-FABP, which is expressed in radial glial cells and Bergman glial cells, functions in maintaining the radial glial fiber system, guiding correct migration of immature neurons, regulating axonal growth, and monitoring synaptic activities and synaptic plasticity. On the other hand, the B-FABP increases the DHA transfer to the neurons. In turn, the DHA enhances the fluidity of the neuronal membrane, increases the reduced GSH levels and reduces LPO and ROS, reduces neuronal apoptosis, and changes certain membrane-bound enzymes activates. The LRPAP-1 functions as a chaperon or escort protein in the intracellular transport of LRP, by preventing it binding to the nascent receptor. As a result, it facilitates the LRP maturity, which is an efflux transporter of AβP, ultimately alleviate the development of senile-related pathophenotypes.

References:

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2. Takeda T. 1999. Senescence-accelerated mouse (SAM): a biogerontological resource in aging research. *Neurobiol Aging.* 20: 105-110.
3. Junutula JR, De Maziere AM, Peden AA, Ervin KE, Advani RJ, van Dijk SM, Klumperman J, Scheller RH. 2004. Rab14 is involved in membrane trafficking between the Golgi complex and endosomes. *Mol Biol Cell.* 15(5): 2218-2229.

Acknowledgements:

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