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The altered transcriptome in aging hippocampus

Abstract

The key role of the hippocampus in age-related cognitive impairments is well known. Invariably, these impairments are accompanied by a neuritic alteration of hippocampal neurons. Here we examine the idea that the structural change is associated with an altered transcriptome, and in this context discuss potential therapeutic interventions.

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Introduction

When considering aging, one particularly interesting brain structure to investigate is the hippocampus. The hippocampal formation includes the subiculum, presubiculum, parasubiculum, entorhinal cortex and hippocampus proper. As part of the limbic system, which plays critical roles in information encoding for short and long term memory, intellectual ability, and spatial navigation, the hippocampal formation is involved in a wide spectrum of the physiological and pathological changes of the aging brain. The hippocampus proper is divided into two main areas:

1. The cornu ammonis (CA; generated from the ammonic neuroepithelium)
2. The dentate gyrus (DG; generated from the primary dentate neuroepithelium)

Their structure and function are particularly vulnerable to senescence. Despite the presence of hippocampal atrophy in many species during aging, there is still considerable controversy on the mechanisms of the altered morphology of this structure which may reflect either the shrinkage of cell body size or the loss of neurons, and may vary depending on the subregions, with CA1 more susceptible to the effects of aging. There is strong evidence supporting neuritic dystrophy/reduced dendritic complexity and dendritic spine irregularity/loss associated with the cognitive deficits of aging. The maintenance of these structures depends on the involvement of distinct transcription factors, neurotrophic factors/glucocorticoids, and related receptors with downstream signaling partners which may be damaged during aging.[1] Indeed, high-performance liquid chromatography separation showed that Protein S100-A9, Neuropilin-1, CRMP1, Myelin protein P2, Tubulin polymerization-promoting protein, Isoform-2 of Vitamin D-binding protein, Neuron-specific calcium binding protein, and Rab-3D (which is critical in neuritic plasticity) are decreased in aged post-mortem human hippocampus.[2] By contrast, the vast majority of proteins – more than 4000 quantified proteins – from aged frontal cortex/hippocampus of mouse remain unchanged.[3] Since the aged hippocampus (dys)function is consistently associated to functional connectivity, network dynamic, and electrophysiological parameters ($Ca^{++}/Na^{+}/K^{+}$ regulation, LTP, potentiation of synaptic activation) mediated by the release of numerous neuromediators (such as acetylcholine, dopamine, norepinephrine, serotonin, GABA, glycine and glutamic acid), it is appealing to review the implication of gene expression underlying the aged-related change within these anatomical sites. Although some of the changes may occur post-translationally, understanding how alteration of various sets of genes expression may be involved in the process of pathological aging may bring insight on neurodegeneration and dementia as well as successful aging. Ultimately, such basic research would also provide new avenues to intervene to protect the aging brain.

Transcriptome response to aging

Characteristics of gene expression have been studied by genome-wide methods, particularly the microarray technology which has been used in the last decade to study the gene expression changes related to human aging using post-mortem tissues or animal models. Data from several original public microarrays offer a reliable analysis of the underlying transcripts associated with aging. Transcriptome changes can reflect activation of pathways specific to senescence or compensatory mechanisms to maintain normal physiological function. Meta-analysis of gene expression in hippocampus has identified different altered transcripts comparing either young and aged, or impaired and unimpaired cognition. In the first case, more than 30 genes are up-regulated, among which ApoE, Rela, S100b, Icam1, Igf1r, Abcc, Alf1, Cds, Actb and Cntn2.[4] These genes are implicated in neuronal formation, survival, migration and axonogenesis. It is tempting to suggest that their up-regulation is associated with the activation of programmed cell survival. Other upregulated genes include inflammatory and immune response and genes associated with the lysosome, known to be elevated during aging, and downregulation of genes involved in energy metabolism. Some genes like the neurotrophins are found altered during aging with learning impairments.[4] However, other microarray analyses have identified different regulated gene sets specifically associated with learning impairments, suggesting that the cognitive deficit does not represent just an exaggerated normal aging process but an alteration of distinct pathways.[5]

Transcriptome in successful aging rat

Previous studies have revealed an interesting feature in inbred LOU/c/jall rat strain.[6] These animals are used as model of healthy aging because of their increased longevity, stable body weight, low incidence of age-related diseases, absence of tumor and maintenance of cognitive performance (recognition memory in this rat strain remain intact up to 42 months of age). They are characterized by intact NMDA-mediated synaptic plasticity in the CA1 hippocampal region, likely due to the maintenance of NMDA receptor activation during aging. In support of this idea, it has been found that mGluR5 and immediate early genes Homer1a and Arc expression associated to cognition are unaltered in aging Lou/c/jall rats as compared to Sprague-Dawley rats. In addition, aging is associated with significantly higher anxiety in rodent and human whereas the level of anxiety is not increased in the aged LOU/c/jall rat strain. This phenotype has been associated with low levels of the stress related Pdyn in the LOU/c/jall hippocampus. Further insight into the nature of specific gene expression has emerged from qRT PCR and extensive microarray assay. In the old LOU/c/jall hippocampus as compared to the old Wistar hippocampus, 15 genes mainly involved in cell adhesion, neuronal action potential propagation, cellular component morphogenesis, signaling transduction and immune system process are significantly altered and may explain the difference in aging between the two strains. Only 9 genes overlapped with the 56 genes overexpressed and 17 genes underexpressed found in a meta-analysis of 27 datasets from mice, rats and humans, looking for common markers of aging.[7]

Concluding remarks

Although we are still far from an integrated and coherent view linking the transcription change to structure alteration, which would provide a potential mean to prevent dystrophic neurons in aging brain, the evidence presented are suggestive for a relationship. Interestingly, we found that the over-expression of an individual gene -CRMP3- in cultured neurons can initiate neurite formation, increase dendrite branching/elongation[8] and also prevent the $PrP^{106-126}$ induced dystrophic changes in dendrites.[9] In human subjects, the extensive neuronal loss associated with the spongiform degeneration of prion pathology affects mostly the basal ganglia and the cerebral and cerebellar cortex. The hippocampal formation, where CRMP3 is highly expressed, is protected until the final stage of disease[10] and the high levels of CRMP3 expression in this area may provide a relative protection of this structure from the disease. These findings suggest that CRMP3 and other neuro-protective molecules may prove useful in the treatment of altered dendritic structure and in the rejuvenation of aging brain in vivo (Quach et al, in preparation).

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Conflict of interest

Author declares there is no conflict of interest in publishing the article.

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