Journal of Scientific Research
Banaras Hindu University, Varanasi

Vol. 60, 2016 : 31-36
ISSN : 0447-9483

IMPACT OF PAX6 ON RAS DEPENDENT CELL SIGNALING IN BRAIN

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Abstract

The Pax6 has been found essential for development, growth and differentiation of cells in brain, eyes, pituitary, pineal gland, and pancreas. Mutations in Pax6 cause aniridia, mental retardation, glucose intolerance and several complications. This review describes association of Pax6 in post-natal development of central nervous system, and aging brain to understand molecular mechanisms of proliferation and differentiation of neuronal cells. Mostly neurons survive for the entire life of an individual but pathways regulating their survival and maintenance are not clear. The presence of Pax6 in the olfactory bulb, amygdala, thalamus, and the cerebellum may serve suitable molecular toggle for cells in the DG, hilar mature neurons, and certain astrocytes of the adult hippocampus. The adult mammalian hippocampus has ability to produce new neurons by progenitor cells residing in well-recognized germinal center which may be regulated by Ras mediated survival of neurons through direct influence on crystallinαA(CryαA).

Signaling in synaptic plasticity of brain

Brain functions are manifested through specific synapses by release of neurotransmitters and other biochemical signals in postsynaptic neurons. One of the most critical events is a rapid and transient rise in calcium levels. The local increase in calcium concentration results in a number of short-term and long-term synapse-specific alterations like insertion or removal of specific calcium channel subunits from the membrane and the post-translational modification or degradation of synaptic proteins (1, 2, 3). Beside these local events at the synapse, elevation of calcium in postsynaptic neurons activates a cascade of signaling events and gene expression essential for neuronal survival, and synaptic plasticity (4, 5). Synaptic plasticity is thought to be crucial for information processing in the brain for learning and memory. Widely studied models for synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). The LTP is a cellular model of learning and memory, which has been described in all excitatory pathways in the hippocampus and other regions of brain. The changes in intracellular calcium levels in neurons are transduced into protein synthesis through activation of specific signalling pathways and transcription factors

for persistent forms of synaptic plasticity, via potential interactions between the mTOR (mammalian target of rapamycin) and ERK pathways in hippocampal neurons (6). The excessive activation of glutamate receptors can also result in neuronal dysfunction and cell death by excitotoxicity (7). These alterations can potentially lead to cell death through different pathways, such as membrane break-down, cytoskeletal alterations, and NO-derived free radical production. Increased activation of glutamate receptors has been described in Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral Sclerosis (ALS), and Hutchinson disease (HD). In recent years, one of the most relevant observations of research on brain indicate age-related cognitive decline not only due to neuronal loss, but the dysfunctions occurring over time (8). The molecular cascades involves activation of protein kinase C pathway, and protein–lipid and protein–protein interactions.

Impact of Pax6 in adult neurogenesis and signaling:

The repair system of central nervous system (CNS) remains on elusive due to poor regenerative capacity and complexity of the CNS. Since the stem cell transplantation offers great promise for repair to neurodegenerative diseases and neurotrauma, biology of neurogenesis, master regulators, and regulation of regulators like Pax6 should be understood. The expression pattern of Pax6 changes considerably after neural tube closure till the cerebral cortex gets specialize and expanded (9). In both human and mouse, the *Pax6* gene contains 16 exons distributed over a 30kb genomic region including alternatively spliced exons *alpha* and 5a (9-12). A number of short range regulatory elements have been identified in the vicinity of the *Pax6* coding region which control tissue-specific *Pax6* expression (13, 14). Some of these elements exhibit overlapping tissue specificity, in eye, telencephalon and diencephalon through cooperative interactions. The immunohistochemical analysis of Pax6 positive cells and expression pattern of Pax6 in olfactory lobe, hippocampus, and cerebellum of aging mouse brain shows progressive reduction in olfactory lobe, cerebellum, and hippocampus from postnatal to old age mice. Modulation in the expression of Pax6 and reduction in Pax6 positive cells show direct association of Pax6 with aging-related neuronal dystrophy (15). Pax6 is required for maintenance of a progenitor cell phenotype (such as *Pax6* in adult neurogenesis) or for maintenance of plasticity in mature neurons in response to environmental stimuli (16). It is also implicated in diseases of CNS, survival of neurons in healthy adult brains and their vulnerability to neurodegeneration because the absence of *Pax6* in postnatal astrocytes reduces their neurogenic potential (17). Additionally, Pax6 regulates survival of dopaminergic periglomerular neurons by inhibiting programmed cell death in these mature olfactory

neurons (18). Tonchev *et al* observed that *Pax6*-expressing neural progenitors survive longer in both the sub granular zone (SGZ) of the hippocampal dentate gyrus (19) and the anterior Sub Ventricular Zone SVZ (20) after experimentally-induced transient global cerebral ischemia in primates.

In humans, heterozygous loss of function mutations of Pax6 cause sight-threatening congenital eye defects, including severe hypoplasia of the iris (aniridia) and retina. These mutations show variable penetrance and expressivity associated with a range of neurological and psychiatric conditions including nystagmus, impaired auditory processing and verbal working memory, autism and mental retardation (21-26) due to structural changes in brain like reduced size of the corpus callosum and anterior commissure, abnormalities of the cerebral cortex and cerebellum and absence of the pineal gland (27, 28). Pax6 mutation has been proposed as a genetic factor for glucose intolerance (29) and genetic deletion of Pax6 in pancreas results in early onset of diabetes in an animal model (30-32). The Pax6 also regulates glucagon gene in response to insulin signaling. Interestingly, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-1 receptor (IGF-1R), have Pax6 binding motifs in their promoter regions (33, 34).

The HOMER3, DNCL1 and TRIM11 show interaction with Pax6 which are associated with development as well as age-related mental disorder, and Alzheimer's disease. The HOMER3, a member of HOMER family of protein, constitutively expresses in the brain and plays role in postsynaptic signaling, axon guidance, and receptor trafficking (35), survival of a neuron, and synaptic connections (36). The combination of depolarization or activation of the cAMP pathway with exposure to a neurotrophic factor increases the survival and growth of neurons (37-40). The cAMP–CREB cascade influences actions of different neurotransmitters, neurotrophic factors, learning and memory in the hippocampus (41, 42). Although the time course for the regulation of learning and memory in both cellular and behavioral models occurs in a much shorter time frame, it is possible that upregulation of cell proliferation enhances the maintenance or processing of memories. The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway), a chain of proteins in the cell that communicates signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. The pathway includes many proteins, including MAPK (mitogen-activated protein kinases, originally called ERK, extracellular signal-regulated kinases), which communicate by adding phosphate groups to a neighboring protein, which acts as an "on" or "off" switch. The Pax6 may serve as a connecting link to regulate both aging and neurodegeneration.

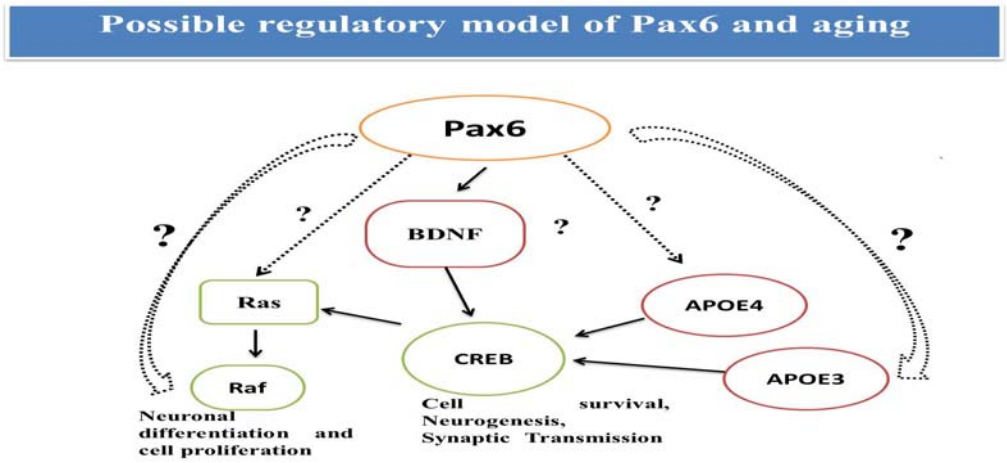

Figure 1: Schematic representation of possible regulatory model of Pax6 and aging.

Conclusion

Most neurons in the adult mammalian brain survive for the entire life of an individual. However, it is unknown that which transcriptional pathways regulate this survival to maintain functional anatomy of healthy brain. Appreciable expression of Pax6 in the olfactory bulb, amygdala, thalamus, and the cerebellum may serve suitable marker for the status of newly generated cells in the DG, hilar mature neurons, and certain astrocytes of the adult hippocampus. The adult mammalian hippocampus has ability to produce new neurons by progenitor cells residing in well-recognized germinal center: the subgranular zone (SGZ) of the dentate gyrus (DG). Pax6 expressed in dopaminergic neurons of the olfactory bulb may regulate the survival of neurons through direct influence on crystallinαA (CryαA).

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