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Research Article

Activating Sleeping Brain Cells- A Paradigm Shift in Dentistry

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Abstract

Background: Neural stem cells (NSC) produce neurons and surrounding glial cells in the brain. The neurons and the glial cells can be regenerated with the further understanding of the mechanism of neural crest cells. Molecules that form a complex called STRIPAK (Striatin Interacting Phosphatase and Kinase) like Mob4 (Monopolar spindle-one binder family member 4), Cka (Connector of kinase to AP1) and PP2A (Protein Phosphatase 2A/Microtubular star, Mts) that promote reactivation in NSCs.

Aim of the Study: To determine how the NSCs work and the role of STRIPAK to make the NSCs either dormant or reactivate them.

Research Question: Is STRIPAK, actually significant in reactivating sleeping brain cells?

Materials and Methods: With taking Medline as a source of research data, articles were selected having undergone randomized controlled trials. Out of these, articles (studies) were chosen which met the criterion for systematic review.

Result: Identification of STRIPAK complex members i.e. Mob4, Cka, and PP2A/Mts;When Mob4 is lost, automatically NSC reactivation is prevented; Mob4 takes care and regulates Hippo pathway and Insulin like receptor cascade (InR/PI3K/Akt) activity in NSCs; Mob4 and Cka act together to reactivate NSCs and hence form a PP2A-Hippo Complex; PP2A inactivates Akt (protein kinaseB) independently of STRIPAK Cka and Mob4 members and maintains quiescent NSCs.

Keywords: Neural Stem Cells (NSC); STRIPAK (Striatin Interacting Phosphatase and Kinase); Mob4 (Monopolar Spindle-One Binder Family Member 4); PP2A (Protein Phosphatase 2A/Microtubular Star, Mts)

Introduction

The practicality and usage of stem cells today is the hotspot of research arena. As all of us are aware that the formation of new neurons and the glial cells by the neural stem cells helps repair the brain homeostasis and any other kind of damage to the brain [1,2]. The human neural stem cells are predominantly found in the Hippocampus and Olfactory bulb area of the brain [3]. The Sub ventricular zone of the forebrain is the most active neurogenetic area and the richest source of neural stem cells. Neural stem cells reactivate only post embryonically and stay dormant until the end of

embryogenesis only to generate neurons and glia of the adult brain [4]. Understanding the mechanism of neural stem cells can help us with therapies that include the glial cells [5]. Hence the aim of the study is to determine how neural stem cells work and the role of STRIPAK as a switch to turn off dormancy/ quiescence and turn on reactivation, with the research question in mind that, "Is STRIPAK actually significant in reactivating sleeping brain cells?"

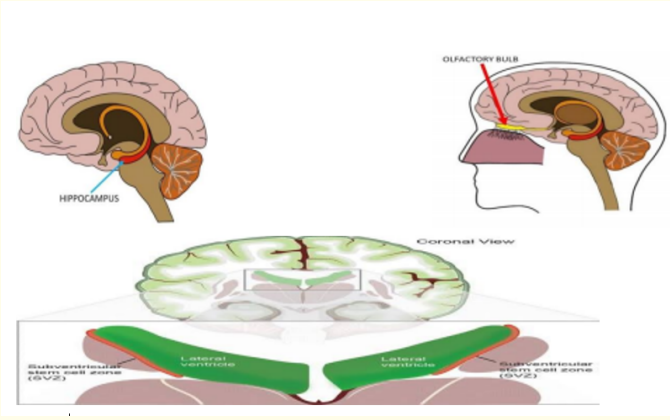

Figure 1

Aim of the Study

To determine how the NSCs work and the role of STRIPAK to make the NSCs either dormant or reactivate them.

Research Question

Is STRIPAK, actually significant in reactivating sleeping brain cells?

Materials and Methods

Many researches and studies have determined that STRIPAK is 100% sensitive and specific [6,7]. Taking the fact into consideration, a literature based systematic review was done to complete the aim with which we started the study. With the Cochrane collaboration taken as reference, about 30 research articles having undergone Randomized controlled trials were chosen for the study, out of which 27 articles were finally selected for having undergone the criterion for systematic review.

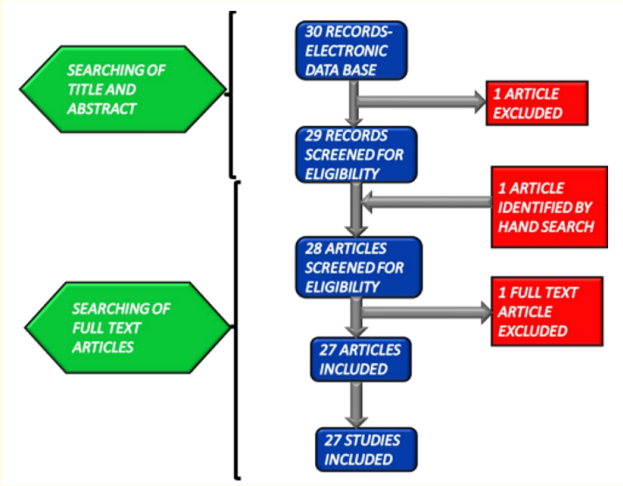

Figure 2

Results

The actual need for this systematic review was laid down on the foundation of the following conclusions which were drawn from the final 27 articles.

The results suggest that the NSC reactivation is based on some of the conserved genes which were exposed due to single cell transcriptome analysis [8]. The analysis reveals transcripts encoding for some of the core STRIPAK complex members:

- Mob4 (Monopolar spindle-one binder family member4)
- Cka (Connector of kinase to AP1), which is the sole Drosophila striatin [9] protein A catalytic subunit of PP2A (Protein Phosphatase 2A/Microtubular star Mts).

Thereby stating that STRIPAK is actually significant [10,11] in reactivating the sleeping brain cells, thereby reaffirming our research question.

Discussion

Recent advances in profiling of the quiescent and NSCs are increasing our understanding regarding these cells [12-14]. Some of the common approaches include brain tissue disassociation [15], cell sorting and culture procedures. The balance between dormancy and reactivation of the NSCs is mainly due to neural replenish-

Figure 3

ment. Here, in the below picture, a sample of the brain from live drosophila considered. It shows the transcript profile between single quiescent versus reactivating NSCs [16,17].

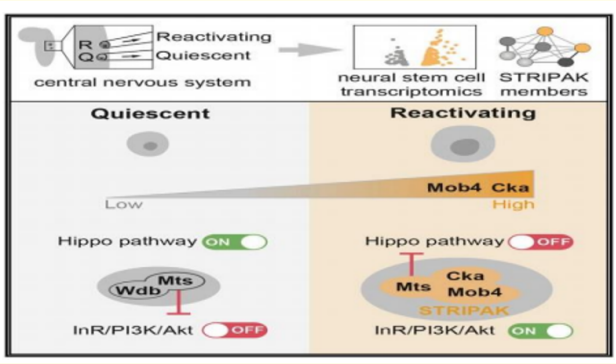

Figure 4

Both quiescence and reactivation in drosophila is dependent on the niche signals. The quiescence in NSC by the niche glia cells is maintained by hippo signaling activation [18,19]. It also proves that the insulin and insulin like growth factor pathway also helps in NSC reactivation. Hence, here, the STRIPAK members i.e. Mob4, Cka and PP2A phosphatase were identified in the analysis. They help in the regulation of NSC quiescence so that they can proceed to the reactivation states and also function as the intrinsic molecular switch in mechanism of InR/PI3k/Akt and Hippo signals [20,21].

The catalytic subunit of PP2A, i.e. Mts helps maintaining NSCs in quiescence, which further prevents the premature phosphorylation of Akt, which is supposed to be a very important component of InR/PI3k/Akt signaling cascade.

Where Mts down regulates the transcript level, Mob4 and Cka up regulates in reacting/s quiescent NSCs. Mob4 and Cka are both very large complexes that are present in fungi to humans containing PPA2. The under expression of these proteins leads to impairment of NSC reactivation, but if overexpressed, they can lead to acceleration of the NSCs [22,23].

STRIPAK/PP2A stops Drosophila Hippo kinase activity via dephosphorylation as it is connected with the hippo in drosophila and mammalian cells [24]. It has been seen that there is cross inhibition between Hippo and InR/PI3K/Akt pathways in both mammalian and Drosophila tissues. Hence, for the physical association of Mts to Hippo and its subsequent inhibition, both Mob4 and Cka are required as reported. PP2A/Mts protein is assembled by the hippo kinase to inactivate the hippo signaling when the Mob4 and Cka start increasing in the NSCs. This can end up turning on the InR/PI3K/Akt and hence behaving as a molecular switch to turn off Hippo signaling.

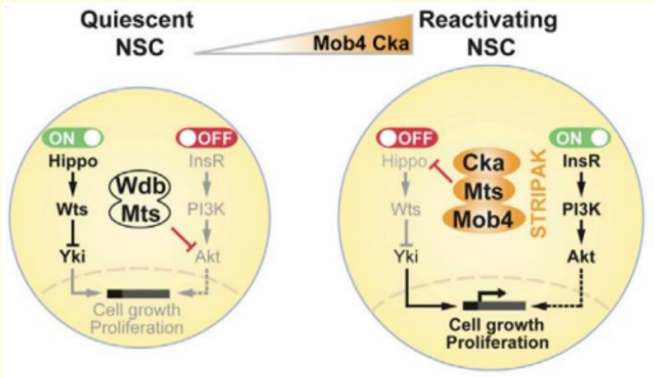

Figure 5

Conclusion

STRIPAK (Striatin interacting phosphatase and kinase) complexes play a crucial role in protein dephosphorylation and also regulates vital signaling pathways like Hippo, Nuclear receptor, MAPK (Mitogen-activated protein kinase) and Cytoskeleton re-

modeling. The STRIPAK complex members that were identified in the Analysis: Mob4, Cka, PP2A/Mts played a significant role in maintaining dormancy/quiescence or turn-on reactivation of Neural stem cells (NSC's). The STRIPAK-PP2A complex containing Mob4 and Cka was found to inhibit Hippo signalling [24] in Drosophila and Mammalian brain cells. The NSC quiescence is done by inactivating Akt where the PP2A/Mts with its regulatory unit Widerborst contributes in the act. Conversely, Mob4 along with Cka aid in forming PP2A-Hippo complex with subsequent Hippo pathway inhibition resulting in reactivation of Neural Stem Cells. Overexpression of Mob4 or its human ortholog MOB4 (hMOB4, also called as Phocein) accelerates Neural Stem Cell reactivation. Thus, increased Mob4 levels accelerate NSC reactivation. Hence, Mob4 functions primarily to promote Neural Stem Cell reactivation [25].

The Hippo pathway play a significant role in Angiogenesis, regulate vascular remodeling and maintain NSCs in dormancy/quiescence. Conversely, activation of Insulin like receptor cascade (InR/PI3K/Akt) results in Neural Stem cell reactivation. When the insulin receptors are activated, they get the PI3K to the cell membrane, which in turn gets Akt protein kinase which is activated by phosphorylation. Therefore, activation of (Insulin like receptor) InR/PI3K/Akt or inhibition of Hippo pathway triggers reactivation of Neural Stem Cells [26].

The Mob4 and Cka play a significant role in protein dephosphorylation by negatively regulating Hippo signaling pathway via the dephosphorylation of Hippo kinase by PP2A phosphatases. Also, depletion of the STRIPAK members reduces the function of Hippo/Mts binding resulting in increased Hippo activation. Hence, it can be said that the Hippo signaling pathway is inactivated by Mob4 and Cka which promote the NSC reactivation and are required for the PP2A-Hippo complex formation. A prolonged Mts inhibition can be thought of if PP2A/Mts would be functioning only in NSC quiescence. But PP2A acts negatively on the insulin receptor signaling cascade, and on the dephosphorylation of Akt as well. Thus, the STRIPAK complex members, Mob4 and Cka targets PP2A/Mts to Hippo, inhibiting Hippo signaling pathway plus activation of InR/PI3K/Akt cascade promoting Neural Stem Cell reactivation.

The different types of STRIPAK complexes are involved in various biological processes such as cell signaling, cell cycle control, apoptosis, cell migration, and tumorigenesis, neural and vascular development [27]. Hence, the STRIPAK (Striatin interacting phosphatase and kinase) complexes do have more number of functions and dysregulation of these complexes are linked to clinical conditions such as cancer. It is of sole importance to determine the role of STRIPAK proteins in regulating other stem cells in the hope of arriving at a potential cure to various clinical conditions for the benefit of mankind.

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