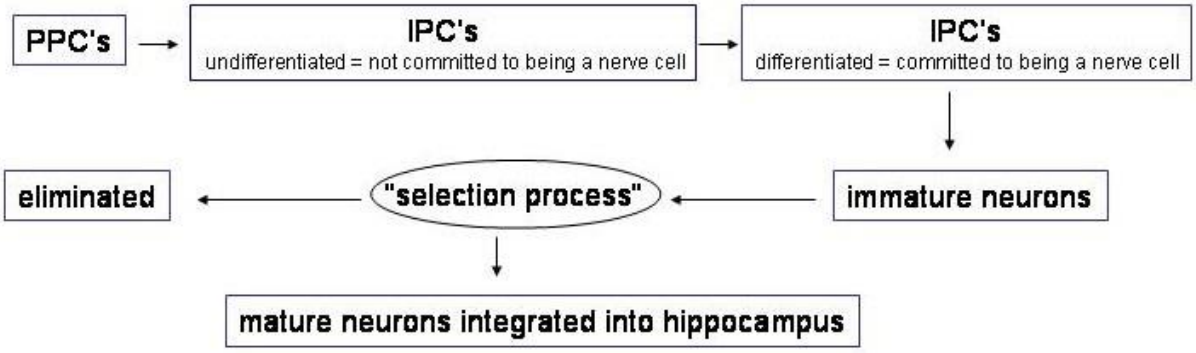
Loss of CDKL5 impairs survival and dendritic growth of newborn neurons by altering AKT/GSK-3β signaling.
Neurobiology of Diseases 2014.

This is a paper from the University of Bologna and the European Molecular Biology Laboratory (EMBL), Monterotondo, Italy. The authors describe studies of the role of the Cdkl5 gene in brain development using knockout mice - that is, mice which have had the Cdkl5 gene removed. Their histological studies focused mainly on a part of the brain called the hippocampal dentate gyrus, because this part of the brain undergoes most of its development after birth which therefore allows for the study of the early development of neurons. The hippocampus also plays a key role in learning and memory.

The development of neurons (nerve cells) in the hippocampus goes through a specific pathway. Cells called primary progenitor cells (PPC's) produce intermediate progenitor cells (IPCs) that are undifferentiated (ie - not yet committed to becoming nerve cells). Undifferentiated IPCs divide and differentiate (specialize) rapidly to form IPCs that are now destined to become nerve cells. These differentiated IPCs will then generate immature neurons that integrate into the neuronal circuits of the hippocampus as mature cells. Most of the immature neurons are subjected to a "selection process", during which they are either recruited or eliminated.



In this study, the authors found that loss of the Cdkl5 gene caused an increase in cell death of immature neurons but with no effect on their preceding IPCs. This suggests that CDKL5 plays an important role in the survival of mature neurons. They also found that KO mice had less neurons, and that dendritic arborization was significantly reduced. This all suggests that the CDKL5 gene also has a role in dendritic development and/or stabilization.

In association with these neuro-anatomical defects, the authors noted that Cdkl5 KO mice exhibited impairment in hippocampus-dependent memory. They also point out that as cortical areas of the brain share these same defects this might explain the severe cognitive impairment of individuals with CDKL5mutations. Finally, the authors propose that the loss of Cdkl5 impairs neurogenesis and dendritic development through disruption of the AKT/GSK-3β signalling pathway.

Note - again, it has taken me a while to digest this paper and I have omitted a lot of detail from my review. We are getting into the nitty-gritty of some of the molecular biology of the CDKL5 protein and I think it is only going to get more complex as further studies emerge. Some of the results in this study looking at the changes in development and appearances of nerve cells confirm other reports. What is new here is that CDKL5 appears to act through the AKT/GSK-3β signalling pathway - although the signalling factor Akt has already been implicated in the role of CDKL5 (see review 20). I have briefly discussed signalling pathways under "Future Research" at the bottom of The CDKL5 Protein. So, we are still only seeing glimpses of the bigger picture which can make it difficult to put into context the results of individual studies such as this one - but still a great study.