CALCINEURIN PRIMES GnRH-SECRETING NEURONS FOR MIGRATION

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In the developing brain, changes in Ca^{2+} transient frequency play a central role in controlling the neuronal cell migration, but the role of this messenger in regulating gene expression is largely unknown. Calcineurin is a Ca^{2+}/calmodulin-dependent phosphatase that acts in a number of cell types to induce short-term and long-term change and has been shown to play a crucial role in the regulation of gene expression. The high abundance of calcineurin in the CNS suggests that this phosphatase might also play a transciptional role in neurons. In order to clarify this issue, we employed GN11 and GT1-7 cells, two different immortalized cell lines that are representative of GnRH neurons at different maturational stages. We found that, in our model, the Ca^{2+}/calcineurin/NFAT pathway is a key player controlling the chemomigratory potential of developing GnRH-secreting neurons. Indeed, pharmacological inhibition of this pathway blocked migration of these cells. Similarly, overactivation by molecular means of this pathway increased migration, while molecular inhibition decreased it. The PI3K pathway did not play a role in controlling migration of these cells under basal conditions. Surprisingly, though, inhibition of the Ca^{2+}/calcineurin/NFAT pathway triggered an activation of this pathway and allowed migration. Our data highlight the "switch" nature of calcineurin, whose activation or inactivation guides cells to proceed from one genetic program to the next (e.g. migration). Furthermore, it also shows that redundant pathways exist in gene expression programs to allow fundamental processes to occur.