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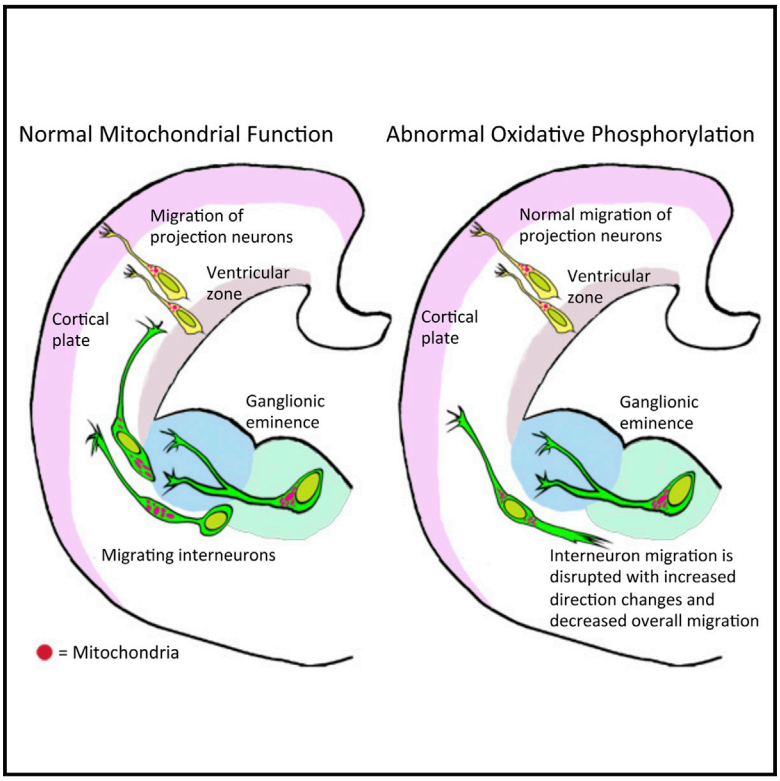
# Differential Mitochondrial Requirements for Radially and Non-radially Migrating Cortical Neurons: Implications for Mitochondrial Disorders

## Graphical Abstract




## Highlights

- Mitochondria in cortical interneurons are motile during migration
- Mitochondria are stationary in migrating cortical projection neurons
- Oxidative phosphorylation defects disrupt cortical interneuron migration
- Interneurons lose polarity when oxidative phosphorylation is perturbed

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## In Brief

Mitochondrial disorders frequently result in neurological dysfunction, but the causes of pathogenesis are uncertain. Lin-Hendel et al. show that mitochondrial dysfunction during neurodevelopment selectively disrupts cortical interneuron migration and not projection neuron migration. They further show a specific dependence on oxidative phosphorylation of interneuron migration.

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# Differential Mitochondrial Requirements for Radially and Non-radially Migrating Cortical Neurons: Implications for Mitochondrial Disorders

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## SUMMARY

**Mitochondrial dysfunction has been increasingly linked to neurodevelopmental disorders such as intellectual disability, childhood epilepsy, and autism spectrum disorder, conditions also associated with cortical GABAergic interneuron dysfunction. Although interneurons have some of the highest metabolic demands in the postnatal brain, the importance of mitochondria during interneuron development is unknown. We find that interneuron migration from the basal forebrain to the neocortex is highly sensitive to perturbations in oxidative phosphorylation. Both pharmacologic and genetic inhibition of adenine nucleotide transferase 1 (Ant1) disrupts the non-radial migration of interneurons, but not the radial migration of cortical projection neurons. The selective dependence of cortical interneuron migration on oxidative phosphorylation may be a mechanistic pathway upon which multiple developmental and metabolic pathologies converge.**

## INTRODUCTION

Mitochondrial diseases (MDs) are the most common inherited metabolic disorder, with an estimated prevalence of 1:5,000 (Schaefer et al., 2004). Although MDs consist of a spectrum of disorders that can involve single or multisystem presentations, neurological symptoms are common clinical characteristics. In recent years, clinical, genetic, and biochemical studies have revealed an emerging link between mitochondrial dysfunction and neurodevelopmental disorders, including intellectual disability (ID) (Valenti et al., 2014), childhood epilepsy (Chevallier et al., 2014), and autism spectrum disorder (ASD) (Rossignol and Frye, 2012). Interestingly, these conditions have also been associated with interneuron dysfunction (Marín, 2012). The correlation between MDs and childhood neurological disorders raises the question as to whether interneuron development is particularly dependent on mitochondrial function.

Recent studies have elucidated roles for mitochondria in multiple aspects of neurodevelopment including neuronal differentiation (Wang et al., 2014), process outgrowth (Cheng et al., 2012; Kimura and Murakami, 2014), and synaptogenesis (Bertholet et al., 2013). Most of these studies have utilized glutamatergic hippocampal neurons as a model, leaving the contribution of mitochondria to interneuron development relatively unexplored. Since interneurons are thought to be a key factor in the pathogenesis of epilepsy and ASD, we were particularly interested in examining mitochondrial behavior and function during developmental processes for which there are distinct features between glutamatergic projection neurons (PNs) and GABAergic interneurons (INs) in the cortex. During development, PNs and INs are derived from distinct locations and take different migration routes: PNs migrate along radial glial fibers from their origin in the dorsal ventricular zone and maintain a relatively stable morphology oriented toward the pial surface (Noctor et al., 2004). In contrast, cortical INs take a circuitous path from their origin in the subcortical ganglionic eminences. Along the way, migrating INs frequently pause, change direction, and exhibit extensive branching dynamics of the leading process (Bellion et al., 2005; Lysko et al., 2011, 2014; Polleux et al., 2002).

Given the greater distance and dynamic nature of IN migration, we reasoned that it requires more energy than does the migration of PNs. First, we found that the mitochondria within INs have a highly dynamic localization pattern during non-radial migration. In contrast, mitochondria remain more consistently localized in radially migrating PNs. Second, we found migrating interneurons to be exquisitely sensitive to agents that block the utilization of ATP generated through oxidative phosphorylation. Remarkably, glycolysis alone is insufficient for normal IN migration but is able to support the radial migration of PNs. Moreover, the genetic disruption of mitochondrial oxidative phosphorylation (OXPHOS) in mice lacking *Ant1* was associated with dramatic alterations of IN migratory morphology and behavior, including mispositioning of the centrosomes. Conversely, *Ant1*$^{-/-}$ PNs appeared normal in our migration assays. These data